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*****STN* Columbus *****
**
FILE 'HOME' ENTERED AT 15:12:44 ON 18 OCT 1999
=> file medline
COST IN U.S. DOLLARS          ENTRY   SESSION   SINCE FILE   TOTAL
FULL ESTIMATED COST          0.27    0.27
FILE 'MEDLINE' ENTERED AT 15:12:49 ON 18 OCT 1999
FILE LAST UPDATED: 14 OCT 1999 (19991014/UP). FILE
COVERS 1960 TO DATE.

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the
Basic Index. See HELP SFIELDS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY
AND ACCURATE
SUBSTANCE IDENTIFICATION.

=> s stroma#(p)exogenous gene or gene construct or vector/ab,bi
'AB' IS NOT A VALID FIELD CODE
26070 STROMA#
0 EXOGENOUS GENE/AB
52796 EXOGENOUS/BI
418026 GENE/BI
140 EXOGENOUS GENE/BI
((EXOGENOUS(W)GENE)/BI)
0 GENE CONSTRUCT/AB
18002 CONSTRUCT/BI
626 GENE CONSTRUCT/BI
0 VECTOR/AB
32375 VECTOR/BI
L1 142 STROMA#(P)EXOGENOUS GENE OR GENE
CONSTRUCT OR VECTOR/AB,BI

=> s il and promoter/ab,bi
'AB' IS NOT A VALID FIELD CODE
0 PROMOTER/AB
68078 PROMOTER/BI

feature
of these cells was their varying capacity to expand cord blood
CD34+
cells. One of these ***stromal*** cell lines ensured more than
twofold
expansion of the initial CD34+CD10-CD19- population in the first
2 weeks
Differentiation toward the B cell lineage was limited, producing
only very
small numbers of CD19+ cells after 6 weeks of culture.

=> s mesenchym/ab,bi
'AB' IS NOT A VALID FIELD CODE
0 MESENCHYM/AB
14675 MESENCHYM/BI
L4 14675 MESENCHYM/AB,BI

=> s l4(p)gene construct or exogenous gene or vector/ab,bi
'AB' IS NOT A VALID FIELD CODE
0 GENE CONSTRUCT/AB
418026 GENE/BI
18002 CONSTRUCT/BI
626 GENE CONSTRUCT/BI
((GENE(W)CONSTRUCT)/BI)
0 EXOGENOUS GENE/AB
52796 EXOGENOUS/BI
418026 GENE/BI
140 EXOGENOUS GENE/BI
((EXOGENOUS(W)GENE)/BI)
0 VECTOR/AB
60999 VECTOR/BI
L5 64 L4(P)GENE CONSTRUCT OR EXOGENOUS GENE
OR VECTOR/AB,BI

=> s l5 and promoter/ab,bi
'AB' IS NOT A VALID FIELD CODE
0 PROMOTER/AB
68078 PROMOTER/BI
L6 12 L5 AND PROMOTER/AB,BI

=> d l- bib ab
YOU HAVE REQUESTED DATA FROM 12 ANSWERS -
CONTINUE? Y(N)y

L6 ANSWER 1 OF 12 MEDLINE
AN 1999257883 MEDLINE
DN 99257883
TI Expression of human bone morphogenic protein 7 in primary
rabbit
periosteal cells: potential utility in gene therapy for osteochondral
repair.
AU Mason J M, Grande D A, Barcia M, Grant R, Pergolizzi R G,
Breitbart A S
CS Department of Research, North Shore University Hospital-New
York
University School of Medicine, Manhasset, USA

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- SO GENE THERAPY, (1998 Aug) 5 (8) 1098-104.  
Journal code: CCE. ISSN: 0969-7128.  
CY ENGLAND: United Kingdom  
DT Journal; Article, (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199908  
EW 19990801  
AB A commonly encountered problem in orthopedics is bone and cartilage tissue injury which heals incompletely or without full structural integrity. This necessitates development of improved methods for treatment of injuries which are not amenable to treatment using current therapies. An already large and growing number of growth factors which play significant roles in bone remodeling and repair have been identified in the past few years. It is well established that bone morphogenic proteins induce the production of new bone and cartilage. An efficient method of delivery of these growth factors by conventional pharmacological means has yet to be elucidated. We wished to evaluate the use of retroviral \*\*\*vector\*\*\* -mediated gene transfer to deliver genes of therapeutic relevance for bone and cartilage repair. To determine the feasibility of using amphotropically packaged retroviral \*\*\*vectors\*\*\* to transduce primary rabbit \*\*\*mesenchymal\*\*\* stem cells of periosteal origin, primary periosteal cells were isolated from New Zealand white rabbits, transduced in vitro with a retroviral \*\*\*vector\*\*\* bearing both the nuclear localized lacZ marker gene and the neo(r) gene, and selected in G418. We used a convenient model for analysis of in vivo stability of these cells which were seeded on to polymer scaffold grafts and implanted into rabbit femoral osteochondral defects. The nuclear localized beta-galactosidase protein was expressed in essentially 100% of selected cells in vitro and was observed in the experimental explants from animals after both 4 and 8 weeks in vivo, while cells transduced with a retroviral \*\*\*vector\*\*\* bearing only the neo(r) gene in negative control explants showed no blue staining. We extended our study by delivering a gene of therapeutic relevance, human bone morphogenic protein 7 (hBMP-7), to primary periosteal cells via retroviral \*\*\*vector\*\*\*. The hBMP-7 gene
- was cloned from human kidney 293 cell total RNA by RT-PCR into a retroviral \*\*\*vector\*\*\* under control of the CMV enhancer/promoter. Hydroxyapatite secretion, presumably caused by overexpression of hBMP-7, was observed on the surface of the transduced and selected periosteal cells; however, this level of expression was toxic to both PA317 producer and primary periosteal cells. Subsequently, the strong CMV enhancer/promoter\*\*\* driving the hBMP-7 gene was replaced in the retroviral \*\*\*vector\*\*\* by a weaker enhancer/promoter\*\*\* from the rat beta-actin gene. Nontoxic levels of expression of hBMP-7 were confirmed at both the RNA and protein levels in PA317 producer and primary periosteal cell lines and cell supernatants. This work demonstrates the feasibility of using a gene therapy approach in attempts to promote bone and cartilage tissue repair using gene-modified periosteal cells on grafts.
- L6 ANSWER 2 OF 12 MEDLINE  
AN 1999230327 MEDLINE  
DN 99230327  
TI Transforming growth factor-beta1 induces interleukin-6 expression via activating protein-1 consisting of JunD homodimers in primary human lung fibroblasts.  
AU Eickelberg O, Pansky A, Musmann R, Bihl M, Tamm M, Hildebrand P, Pernuchoud A P, Roth M  
CS Department of Research and Internal Medicine, University Hospital, 4031 Basel, Switzerland. oliver.eickelberg@yale.edu  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Apr 30) 274 (18) 12933-8.  
Journal code: HIV. ISSN: 0021-9258.  
CY United States  
DT Journal; Article, (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199908  
EW 19990801  
AB Transforming growth factor (TGF)-beta1 induces extracellular matrix deposition and proliferation of \*\*\*mesenchymal\*\*\* cells. We reported that interleukin (IL)-6 is an essential mediator of growth factor-induced proliferation of lung fibroblasts. Here, we demonstrate by
- reverse transcriptase polymerase chain reaction and enzyme-linked immunosorbent assay that TGF-beta1 is a potent inducer of IL-6 mRNA and protein in primary human lung fibroblasts. Transient transfections of fibroblasts with a luciferase reporter \*\*\*gene\*\*\* construct\*\*\* nucleotides -651 to +1 of the human IL-6 \*\*\*promoter\*\*\* TGF-beta1 also potently activated IL-6 \*\*\*promoter\*\*\* activity. Progressive 5'-deletions and site-directed mutagenesis of the parental construct located the TGF-beta1-responsive cis-regulatory element to a known activating protein-1 (AP-1) sequence (nucleotides -284 to -276). Gel shift analyses revealed that AP-1 DNA binding activity in nuclear extracts was increased 30 min after stimulation with TGF-beta1. In contrast, neither CCAAT enhancer-binding protein-beta, NF-kappaB, nor Sp1 were activated by TGF-beta1. Supershift analyses demonstrated that the AP-1 complex induced by TGF-beta1 was composed of Jun isoforms and absent of Fos isoforms. Moreover, this complex was found to be a JunD homodimer. Our data thus demonstrate that TGF-beta1 is a potent inducer of IL-6 in primary human lung fibroblasts. The TGF-beta1-activated JunD homodimer may be essential for a majority of the biological effects induced by TGF-beta1 in this cell type, such as proliferation and extracellular matrix synthesis.
- L6 ANSWER 3 OF 12 MEDLINE  
AN 1999182460 MEDLINE  
DN 99182460  
TI COUP-TF upregulates NGF-A gene expression through an Sp1 binding site.  
AU Pipanon C, Tsai S Y, Tsai M J  
CS Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.  
SO MOLECULAR AND CELLULAR BIOLOGY, (1999 Apr) 19 (4) 2734-45.  
Journal code: NGY. ISSN: 0270-7306.  
CY United States  
DT Journal; Article, (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199906  
EW 19990604  
AB The formation of various tissues requires close communication between two groups of cells, epithelial and \*\*\*mesenchymal\*\*\* cells. COUP-TFs are

transcription factors which have been shown to have functions in embryonic development. COUP-TF1 is expressed mainly in the nervous system, and its targeted deletion leads to defects in the central and peripheral nervous systems. COUP-TF1 is highly expressed in the \*\*\*mesenchymal\*\*\* component of the developing organs. A null mutation of COUP-TF1 results in the malformation of the heart and blood vessels. From their expression pattern, we proposed that COUP-TFs regulate paracrine signals important for \*\*\*mesenchymal\*\*\* cell-epithelial cell interactions. In order to identify genes regulated by COUP-TF in this process, a rat urogenital \*\*\*mesenchymal\*\*\* cell line was stably transfected with a COUP-TF1 expression \*\*\*vector\*\*\*. We found that NGF1-A, a gene with important functions in brain, organ, and vasculature development, has elevated mRNA and protein levels upon overexpression of COUP-TF1 in these cells. A study of the \*\*\*promoter\*\*\* region of this gene identified a COUP-TF-responsive element between positions -64 and -46. Surprisingly, this region includes binding sites for members of the Sp1 family of transcription factors but no COUP-TF binding site. Mutations that abolish the Sp1 binding activity also impair the transactivation of the NGF1-A \*\*\*promoter\*\*\* by COUP-TF. Two regions of the COUP-TF molecule are shown to be important for NGF1-A activation: the DNA binding domain and the extreme C terminus of the putative ligand binding domain. The C-terminal region is likely to be important for interaction with coactivators. In fact, the coactivators p300 and steroid receptor activator 1 can enhance the transactivation of the NGF1-A \*\*\*promoter\*\*\* induced by COUP-TF1. Finally, we demonstrated that COUP-TF can directly interact with Sp1. Taken together, these results suggest that NGF1-A is a target gene for COUP-TFs and that the Sp1 family of transcription factors mediates its regulation by COUP-TFs.

L6 ANSWER 4 OF 12 MEDLINE  
AN 1998389728 MEDLINE  
DN 98389728  
TI Transcriptional activation capacity of the novel PLAG family of

zinc finger proteins  
AU Kao K; Voz M L; Hensen K; Meyen E; Van de Ven W J  
CS Laboratory for Molecular Oncology, Center for Human Genetics, University of Leuven and Flanders Interuniversity Institute for Biotechnology, Herestraat 49, B-3000 Leuven, Belgium.  
koen.kas@med.kuleuven.ac.be  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Sep 4) 273 (36) 23026-32.  
Journal code: HIV. ISSN: 0021-9258.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
OS GENBANK-U81992; GENBANK-AF006003  
EM 199812  
EW 19981203  
AB We have isolated and characterized two novel cDNAs encoding C/2H2 zinc finger proteins showing high sequence homology to PLAG1, a protein ectopically activated by \*\*\*promoter\*\*\* swapping or \*\*\*promoter\*\*\* substitution in pleomorphic adenomas with chromosomal abnormalities at chromosome 8q12. PLAG1 and the two new PLAG1 family members (PLAGL1 and PLAGL2) constitute a novel subfamily of zinc finger proteins that recognize DNA and/or RNA. To examine the potential of the three proteins to modulate transcription, we constructed several binding domain fusion proteins and measured their ability to activate transcription of a reporter \*\*\*gene\*\*\*. \*\*\*construct\*\*\* in different mammalian cell lines and in yeast. Although the carboxyl-terminal part of PLAGL1 shows strong overall transcriptional activity in \*\*\*mesenchymal\*\*\* (COS-1) and epithelial cells (293), both PLAG1 and PLAGL2 transactivate in \*\*\*mesenchymal\*\*\* cells only if depleted from a repressing region. This effect is less profound in epithelial cells. These data suggest that the activation in pleomorphic adenomas of PLAG1 most likely results in uncontrolled activation of downstream target genes.

L6 ANSWER 5 OF 12 MEDLINE  
AN 97444368 MEDLINE  
DN 97444368  
TI Tissue-specific expression of the L1 cell adhesion molecule is modulated by the neural restrictive silencer element.  
AU Kallunki P; Edelman G M; Jones F S

CS Department of Neurobiology, The Scripps Research Institute and The Skaggs Institute for Chemical Biology, La Jolla, California 92037, USA.  
NC HD33576 (NICHID)  
NS34493 (NINDS)  
SO JOURNAL OF CELL BIOLOGY, (1997 Sep 22) 138 (6) 1343-54.  
Journal code: HMV. ISSN: 0021-9525.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Cancer Journals; Priority Journals  
OS GENBANK-U91929  
EM 199712  
AB The cell adhesion molecule L1 mediates neurite outgrowth and fasciculation during embryogenesis and mutations in its gene have been linked to a number of human congenital syndromes. To identify DNA sequences that restrict expression of L1 to the nervous system, we isolated a previously unidentified segment of the mouse L1 gene containing the \*\*\*promoter\*\*\*, the first exon, and the first intron and examined its activity in vitro and in vivo. We found that a neural restrictive silencer element (NRSE) within the second intron prevented expression of L1 gene constructs in nonneural cells. For optimal silencing of L1 gene expression by the NRSE-binding factor RE-1-silencing transcription factor (REST)/NRSF, both the NRSE and sequences in the first intron were required. In transgenic mice, an L1lacZ \*\*\*gene\*\*\* \*\*\*construct\*\*\* with the NRSE generated a neurally restricted expression pattern consistent with the known pattern of L1 expression in postmitotic neurons and peripheral glia. In contrast, a similar construct lacking the NRSE produced precocious expression in the peripheral nervous system and ectopic expression in \*\*\*mesenchymal\*\*\* derivatives of the neural crest and in mesodermal and ectodermal cells. These experiments show that the NRSE and REST/NRSF are important components in restricting L1 expression to the embryonic nervous system.

L6 ANSWER 6 OF 12 MEDLINE  
AN 97059146 MEDLINE  
DN 97059146  
TI Zebrafish Pax9 encodes two proteins with distinct C-terminal transactivating domains of different potency negatively regulated by adjacent N-terminal sequences

AU Nornes S, Mikkola I, Krauss S, Delghandi M, Perander M, Johansen T  
 CS Departments of Biochemistry, Institute of Medical Biology, University of Tromsø, 9037 Tromsø, Norway  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Oct 25) 271 (43) 26914-23.  
 Journal code: HIV. ISSN: 0021-9258  
 CY United States  
 DT Journal Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 OS GENBANK-U40931; GENBANK-U40932  
 EM 199702  
 EW 19970204  
 AB We describe the isolation of cDNA clones for zebrafish Pax9. expression was initiated at the end of the segmentation period in \*\*\*mesenchymal\*\*\* sclerotome cells on both sides of the notochord similarly to the corresponding mouse and chick genes. Two transcripts, Pax9a and -b, are generated by alternative splicing. The gene contains 4 exons with exon 3 being included in the Pax9a transcript and spliced out in the Pax9b transcript. The Pax9a and -b proteins are identical for 212 amino acids from the N terminus but contain distinct C-terminal regions of 131 and 58 amino acids, respectively. The paired domain of Pax9 displayed a binding-site specificity distinct from Pax6 but similar to Pax1 and -2. Both Pax9a and -b activated a \*\*\*promoter\*\*\* containing a paired domain binding site. However, this activation was observed when low amounts of Pax9 expression \*\*\*vectors\*\*\* were used. Higher amounts led to a sharp decrease in the activation and even turned into repression. Both the distinct C-terminal regions of Pax9a and -b harbored transcriptional activating domains of different potency not revealed in the context of the full-length proteins due to a negative influence of the N-terminal region including the paired domain.  
 L6 ANSWER 7 OF 12 MEDLINE  
 AN 96428457 MEDLINE  
 DN 96428457  
 TI The beta 4 integrin subunit is expressed in mouse fibroblasts and modulated by transforming growth factor-beta 1.  
 AU Scardigli R, Soddu S, Falcioni R, Crescenzi M, Cimino L, Sacchi A  
 CS Molecular Oncogenesis Laboratory, Regina Elena Cancer

Institute, C.R.S., Rome, Italy.  
 SO EXPERIMENTAL CELL RESEARCH, (1996 Sep 15) 227 (2) 223-9.  
 Journal code: EPB. ISSN: 0014-4827.  
 CY United States  
 DT Journal Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199701  
 EW 19970104  
 AB Integrin beta 4 subunit is present in association with alpha 6 chain on both normal and transformed epithelial cells. Recently alpha 6 beta 4 heterodimer was found on the endothelium of medium-sized blood vessels and on immature thymocytes. In this report we show, by Northern blotting, indirect immunofluorescence, immunoprecipitation, and Western blotting, that beta 4 subunit is expressed also on cells of \*\*\*mesenchymal\*\*\* origin such as fibroblasts, myoblasts, and myotubes. Increased expression of alpha 6 beta 4 has been related to the aggressive metastatic phenotype of human and murine carcinomas. The transforming growth factor (TGF-beta 1) has been found to modulate the expression of several integrins and intracellular matrix proteins, as well as to stimulate cell invasion and metastatic potential. To evaluate whether alpha 6 beta 4 expression is modulated by TGF-beta 1, we transfected 3T3 fibroblasts with an expression \*\*\*vector\*\*\* carrying the human TGF-beta 1 cDNA driven by the SV40 early \*\*\*promoter\*\*\*. We observed by indirect immunofluorescence a modification in the subcellular distribution of beta 4 subunit, which acquires a perinuclear localization. This finding suggests this integrin subunit correlates with the cytoskeletal reorganization induced by TGF-beta 1.  
 L6 ANSWER 8 OF 12 MEDLINE  
 AN 96330323 MEDLINE  
 DN 96330323  
 TI The paired-box transcription factor, PAX2, positively modulates expression of the Wilms' tumor suppressor gene (WT1).  
 AU Delbi M, Gahremani M, Lechner M, Dressler G, Pelletier J  
 CS Department of Biochemistry, McGill University, Montreal, Quebec, Canada.  
 SO ONCOGENE, (1996 Aug 1) 13 (3) 447-53.  
 Journal code: ONC. ISSN: 0950-9232.  
 CY ENGLAND; United Kingdom

DT Journal Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199611  
 AB The Wilms' tumor suppressor gene, wt1, encodes a zinc finger protein which functions as a transcriptional regulator. Expression of the wt1 gene is developmentally regulated and restricted to a small set of tissues which include the fetal urogenital system, mesothelium, and spleen. In the developing kidney, induction of nephrogenesis by the ureter is accompanied by an increase in expression levels of the Pax-2 gene, a developmentally and spatially regulated paired-box member. This is followed by an increase in wt1 expression as \*\*\*mesenchymal\*\*\* cells condense and differentiate. In this report, we demonstrate that PAX2 isoforms are capable of transactivating the wt1 \*\*\*promoter\*\*\*. Deletion mutagenesis of the wt1 \*\*\*promoter\*\*\* identified an element responsible for mediating PAX2 responsiveness, located between nucleotides -33 and -71 relative to the first wt1 transcription start site. Consistent with its identity as a PAX responsive element, multimerization of this motif upstream of a heterologous minimal \*\*\*promoter\*\*\* enhanced reporter activity when co-transfected with a Pax-2 expression \*\*\*vector\*\*\*. Finally, we demonstrate that PAX2 can stimulate expression of the endogenous wt1 gene. These results suggest that a role for PAX2 during \*\*\*mesenchyme\*\*\*-to-epithelium transition in renal development is to induce wt1 expression.  
 L6 ANSWER 9 OF 12 MEDLINE  
 AN 94109538 MEDLINE  
 DN 94109538  
 TI Regulation of interleukin-1 and tumor necrosis factor-alpha induced granulocyte-macrophage colony-stimulating factor gene expression: potential involvement of arachidonic acid metabolism.  
 AU Rizzo M T, Boswell H S  
 CS Division of Hematology/Oncology, Indiana University School of Medicine, Walter Oncology Center, Indianapolis.  
 SO EXPERIMENTAL HEMATOLOGY, (1994 Jan) 22 (1) 87-94.  
 Journal code: EPR. ISSN: 0301-472X.  
 CY United States  
 DT Journal Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals

EM 199404

AB Signal transduction pathways evoked by interleukin-1 (IL-1) and tumor

necrosis factor-alpha (TNF-alpha) to stimulate expression of other cytokines in \*\*\*mesenchymal\*\*\* cells are not clearly understood.

Stimulation of the murine bone marrow stromal cell line

+/(+)-LDA 11

with IL-1 (500 U/ml) in combination with TNF-alpha (500 U/ml)

(IL-1 plus

TNF-alpha) induced expression of c-jun mRNA as well as

granulocyte-macrophage colony stimulating factor (GM-CSF)

mRNA. We

investigated the possibility that arachidonic acid metabolites, acting through protein Kinase C (PKC) and perhaps also through the

PKC-responsive

transcription factor c-jun/AP-1, may be responsible for regulating

GM-CSF

transcription in these stromal cells. Expression of GM-CSF mRNA

was

preceded by IL-1 plus TNF-alpha induced arachidonate release

(assayed

using the 3H-derivative). Pretreatment of cells with the

phospholipase A2

inhibitor quinacrine (20 microM) inhibited accumulation of both

c-jun and

GM-CSF mRNA but had no influence on expression of other genes

induced by

IL-1 and TNF-alpha, including leukemia inhibitory factor (LIF). In addition, quinacrine partially blocked IL-1 plus TNF-alpha induced 3H-arachidonic acid release from prelabeled stromal cells.

Furthermore,

exogenous arachidonate (10 to 50 microM) induced expression of

c-jun. To

investigate the role of arachidonate in GM-CSF transcription, we

used a

reporter \*\*\*vector\*\*\* consisting of the murine GM-CSF

\*\*\*promoter\*\*\*

linked to firefly luciferase. Transfection efficiency was monitored

by

assessing expression of a constitutively active gene, RSV-beta galactosidase. In this system, quinacrine significantly inhibited IL-1 plus TNF-alpha induced GM-CSF transcription assayed with the reporter

construct. Exogenous arachidonic acid alone (10 microM) increased activity

of GM-CSF reporter \*\*\*vector\*\*\* 1.5-fold over control. These

results

are consistent with the hypothesis that arachidonate metabolites are involved in the signaling pathway that leads to IL-1 plus TNF-alpha induced GM-CSF gene expression. Thus, transcriptional activation of GM-CSF

gene is mediated, in part, by the arachidonate cascade.

L6 ANSWER 10 OF 12 MEDLINE

AN 93275635 MEDLINE

DN 93275635

TI Resistance of human fibroblasts to c-fos mediated transformation.

AU Alt M; Grassmann R

CS Institut für Klinische und Molekulare Virologie, Universitat

Erlangen-Nürnberg, Germany

SO ONCOGENE, (1993 Jun) 8 (6) 1421-7.

Journal code: ONC. ISSN: 0950-9232.

CY ENGLAND; United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199309

AB Overexpression of the proto-oncogene c-fos induces

transformation of

primary avian and established rodent \*\*\*mesenchymal\*\*\* cells and tumor

development in transgenic mice. As overexpression of Fos was also

found in

several human tumors of \*\*\*mesenchymal\*\*\* origin, we were

interested

whether c-fos is a transforming protein for human cells. Since fos

genes

transduced by infection competent \*\*\*vectors\*\*\* were most

efficient in

cellular transformation, expression cassettes of the human c-fos

were

introduced into a replication competent herpesvirus saimiri

\*\*\*vector\*\*\*

. Infection of human neonatal fibroblasts, cells of

\*\*\*mesenchymal\*\*\*

origin, resulted in episomal persistence of the recombinant viral

genome

and expression of c-fos in high excess. However careful

examination for

transformed phenotype failed to detect any changes in morphology.

serum

dependence, anchorage dependence, and life span, suggesting

resistance of

human \*\*\*mesenchymal\*\*\* cells against c-fos mediated

transformation.

L6 ANSWER 11 OF 12 MEDLINE

AN 92049310 MEDLINE

DN 92049310

TI The encephalomyocarditis virus internal ribosome entry site

allows

efficient coexpression of two genes from a recombinant provirus in

cultured cells and in embryos.

AU Chattas I R; Sanes J R; Majors J E

CS Department of Biochemistry and Molecular Biophysics,

Washington University

School of Medicine, St. Louis, Missouri 63110.

SO MOLECULAR AND CELLULAR BIOLOGY, (1991 Dec) 11

(12) 5848-59.

Journal code: NGY. ISSN: 0270-7306

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199202

AB Rous sarcoma virus-based retroviral \*\*\*vectors\*\*\* were

constructed to

compare three different approaches for coexpressing two genes in individual infected cells. All \*\*\*vectors\*\*\* expressed the

upstream

gene (lacZ) from the Rous sarcoma virus long terminal repeat, while the

downstream gene (the chloramphenicol acetyltransferase gene [cat]

or

v-src) was expressed in one of three ways: from a subgenomic

mRNA

generated by regulated splicing, from a strong internal

\*\*\*promoter\*\*\*

, or from the encephalomyocarditis virus internal ribosome entry

site

(IRES). Both biochemical and immunohistochemical assays of

cultured cells

showed that the encephalomyocarditis virus IRES provided the

most

efficient means for coexpressing two genes from a single provirus.

Most

importantly, most cells infected by a LacZ-IRES-CAT virus

expressed both

LacZ and CAT, whereas most cells infected by internal

\*\*\*promoter\*\*\*

or regulated splicing \*\*\*vectors\*\*\* expressed either LacZ or

CAT but

not both. In addition, viral titers were highest with IRES

\*\*\*vectors\*\*\*

. Presumably, use of the IRES avoids transcriptional controls and

RNA

processing steps that differentially affect expression of multiple

genes

from internal \*\*\*promoter\*\*\* and regulated splicing

\*\*\*vectors\*\*\*

Finally, we injected a LacZ-IRES-v-Src virus into chicken embryos

and then

identified the progeny of infected cells with a histochemical stain

for

LacZ. LacZ-positive cells in both skin and \*\*\*mesenchyme\*\*\*

displayed

morphological abnormalities attributable to expression of v-src.

Thus,

IRES \*\*\*vectors\*\*\* can be used to coexpress a reporter gene

and a

bioactive gene in vivo.

L6 ANSWER 12 OF 12 MEDLINE

AN 89291870 MEDLINE

DN 89291870

TI Characterization of the \*\*\*promoter\*\*\* region of the human thrombospondin gene. DNA sequences within the first intron increase

transcription.

AU Laherty C D; Gierman T M; Dixit V M

CS Department of Pathology, University of Michigan Medical School, Ann Arbor, 48109

NC HL39037 (NHLBI)

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1989 Jul 5) 264 (19) 11222-7

Journal code: HIV. ISSN: 0021-9258.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

OS GENBANK-104835

EM 198910

AB Thrombospondin (TSP) is an extracellular matrix glycoprotein whose synthesis and secretion by \*\*\*mesenchymal\*\*\* cells is regulated at the level of gene transcription by platelet-derived growth factor. To examine the transcriptional regulation of the TSP gene at the molecular level, a genomic clone containing the human TSP \*\*\*promoter\*\*\* and flanking sequence was isolated and characterized. A 3.8-kilobase pair (kb) DNA fragment containing the first three exons, the first two introns, and 2.2 kb of 5'-flanking region was sequenced, and the site of transcription initiation was determined by both primer extension and S1 nuclease mapping. Consensus sequences for several potential regulatory elements were found in the 5'-flanking sequence, including a TATA box consensus sequence, TTTTAAAA, located 24 base pairs upstream from the transcription start site. A chimeric gene was constructed containing the first intron, the first exon, and 2.0 kb of 5'-flanking sequence of the TSP gene fused to the promoterless gene for chloramphenicol acetyltransferase. When transfected into COS-1 or NIH3T3 cells this \*\*\*gene\*\*\* \*\*\*construct\*\*\* was transcribed, indicating the presence of a functional \*\*\*promoter\*\*\* in the TSP sequence. Transient transfection studies using deletion mutants of this TSP-chloramphenicol acetyltransferase construct were performed to locate cis-acting regulatory sequences. The flanking sequence 5' to position -234 had little or no effect on transcriptional activity, whereas deletion of 5'-flanking sequence extending further in the 3' direction resulted in the gradual loss of transcriptional activity. The removal of the first intron resulted in a 4-fold decrease in transcript levels, indicating the presence of a cis-acting positive element(s) in the first intron of the human TSP gene.

This element(s) was further localized to the region between position +576 and position +727.

=> s stromal fibroblast#ab,bi  
'AB' IS NOT A VALID FIELD CODE  
0 STROMAL FIBROBLAST#AB  
16247 STROMAL/BI  
92189 FIBROBLAST#BI  
443 STROMAL FIBROBLAST#BI  
((STROMAL(W)FIBROBLAST#BI)  
L7 443 STROMAL FIBROBLAST#AB,BI

=> s l7(pXvector# or construct#)ab,bi  
'AB' IS NOT A VALID FIELD CODE  
0 VECTOR#AB  
60999 VECTOR#BI  
0 CONSTRUCT#AB  
27034 CONSTRUCT#BI  
L8 11 L7(PXVECTOR# OR CONSTRUCT#)AB,BI

=> d 1 - bib ab  
YOU HAVE REQUESTED DATA FROM 11 ANSWERS -  
CONTINUE? Y(N)Y

L8 ANSWER 1 OF 11 MEDLINE  
AN 199086465 MEDLINE  
DN 99086465  
TI Efficient gene transfer into normal human skeletal cells using recombinant adenovirus and conjugated adenovirus-DNA complexes.  
AU Sommer B; Kuznetsov S A; Robey P G; O'Connell B; Cristiano R J; Young M F  
CS Craniofacial and Skeletal Diseases Branch, Building 30, Room 228, National Institute of Dental Research, National Institutes of Health, Bethesda, MD 20892, USA.  
SO CALCIFIED TISSUE INTERNATIONAL, (1999 Jan) 64 (1) 45-9.  
Journal code: CGH. ISSN: 0171-967X.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199905  
EW 19990503  
AB In order to assess efficient DNA gene transfer into human primary cell cultures derived from the skeleton we tested two viral-based procedures.  
First, replication-deficient recombinant adenoviruses (ADV) were used to infect post-confluent human marrow \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* (HMSF) and human trabecular bone (HTB) cells. Both cell types

were readily infected by modified adenoviral \*\*\*vectors\*\*\* carrying a reporter gene making this virus an attractive candidate to facilitate DNA gene transfer.  
In a second approach we coinubated DNA with ADV that had polylysine (PLL) covalently attached. With this ADV/PLL/DNA complex, very efficient gene transfer into multilayered HMSF and HTB cell cultures was observed, and DNA coinubated with unmodified ADV failed to be effectively transferred.  
These data imply that the covalently bound PLL more effectively binds exogenous DNA, resulting in a highly efficient internalization event in both cell types. Thus, this latter method has many advantages over conventional ADV gene transfer procedures. It is simple, rapid, and it does not require engineering of DNA into the viral genome, thereby allowing transfer of large fragments of DNA.

L8 ANSWER 2 OF 11 MEDLINE  
AN 1998109431 MEDLINE  
DN 98109431  
TI Endothelial cell-specific expression of tumor necrosis factor-alpha from the KDR or E-selectin promoters following retroviral delivery.  
AU Jaggar R T; Chan H Y; Harris A L; Bicknell R  
CS Imperial Cancer Research Fund Molecular Oncology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, UK.  
SO HUMAN GENE THERAPY, (1997 Dec 10) 8 (18) 2239-47.  
Journal code: A12. ISSN: 1043-0342.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199804  
EW 19980404  
AB The tumor vasculature offers a target for anti-cancer gene therapy which has the advantages both of good accessibility to systemically delivered therapy and comparative homogeneity across solid tumor types. We aimed to develop retroviruses carrying endothelial-specific promoters for the delivery of genes to proliferating endothelial cells in vitro and to endothelial cells in vivo. This paper reports the generation of such retroviral \*\*\*vectors\*\*\* and the level of expression of murine tumor necrosis factor-alpha (mTNF-alpha) cDNA following infection into endothelial cells and \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\*.  
Retroviral

\*\*\*vectors\*\*\* carrying mTNF-alpha have been generated whose expression is controlled either by the retroviral long terminal repeat or by 5' proximal promoter sequences from the endothelial-specific kinase insert domain receptor (KDR)/VEGF receptor and E-Selectin promoters within the context of a self-inactivating (SIN) \*\*\*vector\*\*\* backbone. Both KDR and E-Selectin have been shown to be upregulated on tumor endothelium. A putative polyadenylation sequence AAATAAA within the E-Selectin promoter was mutated to permit faithful transmission of retroviral \*\*\*vectors\*\*\* carrying this promoter. We demonstrate a 10- to 11-fold increase in mTNF-alpha expression from promoter elements within sEND endothelioma cells as compared to NIH-3T3 fibroblasts. Suggestions for further improvements in \*\*\*vector\*\*\* design are discussed.

L8 ANSWER 3 OF 11 MEDLINE  
AN 97322109 MEDLINE  
DN 97322109  
TI Differential regulation of interstitial collagenase (MMP-1) gene expression by ETS transcription factors.  
AU Westernmark J, Seth A, Kahan V M  
CS Department of Dermatology, Turku University Central Hospital, Finland  
SO ONCOGENE, (1997 Jun 5) 14 (22) 2651-60.  
Journal code: ONC. ISSN: 0950-9232.

CY ENGLAND; United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199709  
EW 19970902  
AB Expression of interstitial collagenase (MMP-1) has been detected in \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* of various malignant tumors. Here, we have studied the effect of three structurally different ETS transcription factors (ETS-1, ERGB/Fli-1, and PU.1) on MMP-1 promoter activity in NIH3T3 fibroblasts. ETS-1 increased the activity of 3.8 kb

MMP-1 promoter \*\*\*construct\*\*\* up to tenfold, while ERGB/Fli-1 or PU.1 alone had no marked effect on basal promoter activity. ETS-1 also markedly potentiated enhancement of MMP-1 promoter by both c-Jun and JunB, whereas ERGB/Fli-1 augmented only the effect of c-Jun. Interestingly, PU.1 abolished induction of MMP-1 promoter by both c-Jun and JunB. Stimulation of MMP-1 promoter by 12-O-tetradecanoyl phorbol-13-acetate and okadaic

acid was differentially augmented by ETS-1 and ERGB/Fli-1, and abrogated by PU.1. Co-transfection studies with MMP-1 promoter 5'-deletion \*\*\*constructs\*\*\* revealed that AP-1 site was necessary for PU.1-elicited suppression. As compared to control cell lines, PU.1-positive stable cells exhibited clearly weaker binding of c-Jun and JunD containing AP-1 complexes to MMP-1 promoter AP-1 element, as well as marked reduction in basal level and induction of c-jun mRNA by 12-O-tetradecanoyl phorbol-13-acetate and okadaic acid, suggesting a novel mechanism for PU.1-mediated inhibition of AP-1 dependent gene expression. These results show that three structurally distinct ETS transcription factors differently modulate AP-1 dependent upregulation of MMP-1 gene expression.

L8 ANSWER 4 OF 11 MEDLINE  
AN 97278888 MEDLINE  
DN 97278888  
TI Bone formation in vivo: comparison of osteogenesis by transplanted mouse and human marrow stromal fibroblasts.  
AU Krebsbach P H, Kuznetsov S A, Satomura K, Emmons R V, Rowe D W, Robey P G  
CS Laboratory of Developmental Biology and Bone Research Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland 20892, USA.  
SO TRANSPLANTATION, (1997 Apr 27) 63 (8) 1059-69.  
Journal code: WEJ. ISSN: 0041-1337.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199707  
EW 19970703  
AB BACKGROUND: Marrow \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* (MSFs) are known to contain bone precursor cells. However, the osteogenic potential of human MSFs has been poorly characterized. The aim of this study was to compare the osteogenic capacity of mouse and human MSFs after implantation in vivo. METHODS: After in vitro expansion, MSFs were loaded into a number of different vehicles and transplanted subcutaneously into immunodeficient mice. RESULTS: Mouse MSFs transplanted within gelatin, polyvinyl sponges, and collagen matrices all formed a capsule of cortical-like bone surrounding a cavity with active hematopoiesis. In transplants of

MSFs from transgenic mice harboring type I procollagen-chloramphenicol acetyltransferase \*\*\*constructs\*\*\*, chloramphenicol activity was maintained for up to 14 weeks, indicating prolonged bone formation by transplanted MSFs. New bone formation by human MSFs was more dependent on both the in vitro expansion conditions and transplantation vehicles. Within gelatin, woven bone was observed sporadically and only after culture in the presence of dexamethasone and L-ascorbic acid phosphate magnesium salt n-hydrate. Consistent bone formation by human MSFs was achieved only within vehicles containing hydroxyapatite/tricalcium phosphate ceramics (HA/TCP) in the form of blocks, powder, and HA/TCP powder-type I bovine fibrillar collagen strips, and bone was maintained for at least 19 weeks. Cells of the new bone were positive for human osteonectin showing their donor origin. HA/TCP powder, the HA/TCP powder-type I bovine fibrillar collagen strips, and powder held together with fibrin were easier to load and supported more extensive osteogenesis than HA/TCP blocks and thus may be more applicable for therapeutic use. CONCLUSIONS: In this article, we describe the differences in the requirements for mouse and human MSFs to form bone, and report the development of a methodology for the consistent in vivo generation of extensive bone from human MSFs.

L8 ANSWER 5 OF 11 MEDLINE  
AN 96316852 MEDLINE  
DN 96316852  
TI Synthesis and secretion of transforming growth factor beta isoforms by primary cultures of human breast tumour fibroblasts in vitro and their modulation by tamoxifen.  
AU Benson J R, Wakefield L M, Baum M, Colletta A A  
CS Hartwell Laboratory, Section of Academic Surgery, Royal Marsden Hospital, London, UK.  
SO BRITISH JOURNAL OF CANCER, (1996 Aug) 74 (3) 352-8.  
Journal code: AV4. ISSN: 0007-0920.  
CY SCOTLAND; United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199611  
AB Tamoxifen may mediate its effect in early breast cancer in part

via an  
 oestrogen receptor (ER)-independent pathway by directly  
 stimulating  
 fibroblasts to produce the negative paracrine growth factor  
 transforming  
 growth factor (TGF)-beta. We have previously shown that secretion  
 of this  
 factor is induced 3-to 30-fold in human fetal fibroblasts in vitro, and  
 by  
 \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* in vivo following  
 tamoxifen  
 treatment of ER-positive and ER-negative breast cancer patients.  
 Primary  
 cultures of breast tumour fibroblasts have been exposed to  
 tamoxifen for  
 48 h, and rates of secretion of TGF-beta 1 and TGF-beta 2  
 measured using a  
 quantitative immunoassay. Fibroblast strains derived from  
 malignant and  
 benign tumours produced and secreted similar amounts of  
 TGF-beta 1, but  
 benign breast tumour fibroblasts secreted significantly higher levels  
 of  
 TGF-beta 2 compared with fibroblasts of malignant origin.  
 Tamoxifen did  
 not induce any consistent increase in TGF-beta secretion into the  
 conditioned medium, but immunofluorescence analysis for the  
 intracellular  
 form of TGF-beta 1 revealed evidence of increased  
 immunoreactive protein  
 in tamoxifen-treated fibroblasts, which is localised to the nucleus.  
 Therefore synthesis of TGF-beta 1 appears to be stimulated by  
 tamoxifen,  
 but increased secretion may be abrogated in vitro. Furthermore,  
 using  
 immunocytochemistry and transient transfection with an  
 ER-responsive  
 reporter \*\*\*construct\*\*\*, no ER was demonstrable in these  
 fibroblasts  
 supporting the proposed ER-independent paracrine pathway.

L8 ANSWER 6 OF 11 MEDLINE  
 AN 95399753 MEDLINE  
 DN 95399753  
 TI Heparin inhibits the expression of interleukin-11 and granulocyte-  
 macrophage colony-stimulating factor in primate bone marrow  
 stromal  
 fibroblasts through mRNA destabilization.  
 AU Yang L, Yang Y C  
 CS Department of Biochemistry, Walther Oncology Center, Indiana  
 University  
 School of Medicine, Indianapolis 46202, USA..  
 NC R01DK43105 (NIDDK)  
 R01HL48819 (NHLBI)  
 SO BLOOD, (1995 Oct 1) 86 (7) 2526-33.  
 Journal code: A8G. ISSN: 0006-4971.  
 CY United States

DT Journal Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abstracted Index Medicus Journals; Priority Journals; Cancer  
 Journals  
 EM 199512  
 AB Interactions between different cytokines, extracellular matrix  
 components,  
 and various cell types inside the bone marrow microenvironment  
 are  
 believed to play important roles in the regulation of hematopoiesis.  
 We  
 observed that both interleukin-1 (IL-1) and  
 12-O-tetradecanoylphorbol-13-  
 acetate (TPA) can stimulate the expression of IL-11 and  
 granulocyte-macrophage colony-stimulating factor (GM-CSF)  
 genes in a  
 primate bone marrow \*\*\*stromal\*\*\* \*\*\*fibroblast\*\*\* cell  
 line.  
 PU-34 We also found that IL-1 or TPA-stimulated IL-11 and  
 GM-CSF  
 expression in PU-34 cells can be abolished by heparin, a class of  
 molecules related to extracellular matrix components,  
 glycosaminoglycans.  
 Because the growth inhibitory signals provided by extracellular  
 factors  
 were less understood, the mechanisms of heparin inhibition of  
 IL-11 and  
 GM-CSF gene expression were further investigated. Our data  
 demonstrate for  
 the first time that heparin did not alter the transcription of  
 endogenous  
 IL-11 and GM-CSF genes or an exogenous IL-11 promoter  
 \*\*\*construct\*\*\*  
 containing an AP-1 sequence. Instead, heparin facilitated the  
 degradation  
 of the corresponding mRNAs. Through RNA gel shift assays,  
 heparin-mediated  
 mRNA destabilization was tentatively linked to its competition for  
 mRNA  
 binding proteins both in the cell-free system and in intact cells.  
 Collectively, our findings suggest that varying degrees of heparin  
 inhibition may provide a novel mechanism for the regulation of  
 cytokine  
 expression during the growth and differentiation of different  
 lineages of  
 hematopoietic cells.

L8 ANSWER 7 OF 11 MEDLINE  
 AN 95263438 MEDLINE  
 DN 95263438  
 TI Cloning and characterization of the promoter region of the human  
 keratinocyte growth factor gene.  
 AU Finch P W; Lengel C; Chedid M  
 CS Department of Clinical Neuroscience, Brown University, Rhode  
 Island  
 Hospital, Providence, USA.  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 May 12)

270 (19) 11230-7.  
 Journal code: HIV. ISSN: 0021-9258.  
 CY United States  
 DT Journal Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 OS GENBANK-U24106  
 EM 199508  
 AB Keratinocyte growth factor (KGF), a member of the fibroblast  
 growth factor  
 family of related proteins, is expressed by \*\*\*stromal\*\*\*  
 \*\*\*fibroblasts\*\*\* and acts on epithelial cells in a paracrine  
 fashion.  
 To understand the mechanisms responsible for regulating normal  
 KGF  
 expression and how these might be altered in disease, the  
 5'-flanking  
 region of this gene was cloned. The presence of two KGF  
 transcription  
 initiation sites was suggested by ribonuclease protection assay and  
 confirmed by primer extension analysis. Examination of the  
 genomic DNA  
 sequence revealed the presence of the putative promoter sequences  
 TATTTA  
 and CCAAT, located 31 and 50 base pairs upstream, respectively,  
 from the  
 first of the two mRNA start points, and putative initiator sequences  
 surrounding each transcription start site. Transient transfection into  
 murine NIH/3T3 fibroblasts demonstrated that the region required  
 for basal  
 level KGF promoter activity was located between bases -225 and  
 +190.  
 Inclusion of sequences between -1503 and -775 markedly reduced  
 promoter  
 activation, indicating the presence of negative regulatory element(s)  
 in  
 this region. A similar pattern of promoter activation was detected in  
 human fibroblasts and in murine C2C12 myoblasts. In contrast, no  
 chromatinol acetyltransferase activity was observed in  
 epithelial and lymphoid cells transfected with the same  
 \*\*\*constructs\*\*\*.  
 Northern blot analysis revealed a strong correlation between KGF  
 RNA  
 expression and promoter activation in all cells tested. Activation of  
 the  
 KGF promoter could be induced by the proinflammatory cytokines  
 interleukin  
 1 and interleukin 6 and by the adenylate cyclase activator forskolin.  
 Taken together, these results indicate the existence of cis-acting  
 element(s) responsible for selective activation of the KGF  
 promoter only  
 in cells that express KGF mRNA and may provide a mechanistic  
 basis for KGF  
 gene expression during inflammation.

L8 ANSWER 8 OF 11 MEDLINE



- AN 95098019 MEDLINE  
DN 95098019  
TI Spontaneous in vitro immortalization of breast epithelial cells from a patient with Li-Fraumeni syndrome.  
AU Shay J W, Tomlinson G, Piatyszek M A, Gollahon L S  
CS Department of Cell Biology and Neurosciences, University of Texas  
Southwestern Medical Center at Dallas 75235-9039.  
NC CA50195 (NCI)  
CA64871 (NCI)  
SO MOLECULAR AND CELLULAR BIOLOGY, (1995 Jan) 15 (1) 425-32.  
Journal code: NGY. ISSN: 0270-7306.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199503  
AB Individuals with germ line mutations in the p53 gene, such as Li-Fraumeni syndrome (LFS), have an increased occurrence of many types of cancer, including an unusually high incidence of breast cancer. This report documents that normal breast epithelial cells obtained from a patient with LFS (with a mutation at codon 133 of the p53 gene) spontaneously immortalized in cell culture while the breast \*\*\*stromal\*\*\*  
\*\*\*fibroblasts\*\*\* from this same patient did not. Spontaneous immortalization of human cells in vitro is an extremely rare event. This is the first documented case of the spontaneous immortalization of breast epithelial cells from a patient with LFS in culture. LFS patient breast \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* infected with a retroviral \*\*\*vector\*\*\* containing human papillomavirus type 16 E7 alone were able to immortalize, whereas stromal cells obtained from patients with wild-type p53, similarly infected with human papillomavirus type 16 E7, did not. The present results indicate a protective role of normal pRB-like functions in breast \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* but not in breast epithelial cells and reinforces an important role of wild-type p53 in the regulation of the normal growth and development of breast epithelial tissue.
- L8 ANSWER 9 OF 11 MEDLINE  
AN 95010359 MEDLINE  
DN 95010359  
TI Basement membrane assembly and differentiation of cultured corneal cells: importance of culture environment and endothelial cell interaction.  
AU Zieske J D, Mason V S, Wasson M E, Meunier S F, Nolte C J, Fukui N, Olsen  
B R, Parenteau N L  
CS Schepens Eye Research Institute, Harvard Medical School, Boston, Massachusetts 02114.  
NC 9014 (NEI)  
R01 EY07334 (NEI)  
R01 EY05665  
SO EXPERIMENTAL CELL RESEARCH, (1994 Oct) 214 (2) 621-33.  
Journal code: EPB. ISSN: 0014-4827.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199501  
AB A three-dimensional corneal tissue \*\*\*construct\*\*\* was used to examine the effect of culture environment and endothelial cell interaction on epithelial differentiation and basement membrane assembly. Rabbit corneal epithelial cells were cultured over rabbit \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* in a collagen matrix with or without an underlying layer of immortalized mouse corneal endothelial cells (Muragaki, Shiota, Inoue, Ooshima, Olsen, and Ninomiya. (1992) Eur. J. Biochem. 207: 895-902). The cultures were grown submerged or at a dry or moist interface. Basement membrane, anchoring fibril, and hemidesmosome assembly was monitored using transmission electron microscopy as well as indirect immunofluorescence microscopy of laminin, type VII collagen, and alpha 6 integrin. Antibodies against keratin 3 (K3) and alpha-enolase marked differentiated and undifferentiated corneal epithelial cells, respectively. When all three cell types were cultured at a moist interface, hemidesmosomes, anchoring fibrils, and a continuous basement membrane were observed 2 wk after lifting the cultures to an air-liquid interface (air-lift). The distribution of alpha-enolase and K3 was identical to patterns seen in the limbal region of the cornea. Air-lifted tissue \*\*\*constructs\*\*\* lacking the endothelial cell layer showed only limited distribution of laminin and type VII collagen at the epithelial-matrix junction. alpha 6 Integrin was present along the entire plasma membrane of the basal cells; epithelial differentiation was not complete as alpha-enolase was seen in basal and two to three layers of suprabasal cells. Submerged cultures without endothelial cells did not
- express differentiation markers or basement membrane components. These data indicate that endothelial cell interaction dramatically enhances the amount and quality of epithelial basement membrane assembly and that epithelial differentiation is influenced by the type of interface between tissue, liquid, and air.
- L8 ANSWER 10 OF 11 MEDLINE  
AN 94260266 MEDLINE  
DN 94260266  
TI Antibody targeting in metastatic colon cancer: a phase I study of monoclonal antibody F19 against a cell-surface protein of reactive tumor stromal fibroblasts.  
AU Welt S, Divgi C R, Scott A M, Ganin-Chesa P, Finn R D, Graham M, Carswell E A, Cohen A, Larson S M, Old L J, et al  
CS Ludwig Institute for Cancer Research, New York Unit, NY.  
NC CA-08748 (NCI)  
CA-57486 (NCI)  
CA-33049 (NCI)  
SO JOURNAL OF CLINICAL ONCOLOGY, (1994 Jun) 12 (6) 1193-203.  
Journal code: JCO. ISSN: 0732-183X.  
CY United States  
DT (CLINICAL TRIAL, PHASE I)  
(CLINICAL TRIAL, PHASE I)  
(CONTROLLED CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199409  
AB PURPOSE: To define the toxicity, imaging, and biodistribution characteristics of iodine 131-labeled monoclonal antibody F19 (131I-mAbF19). MAbF19 recognizes the fibroblast activation protein (FAP), a cell-surface glycoprotein not present in most normal tissues, but abundantly expressed by reactive \*\*\*stromal\*\*\*  
\*\*\*fibroblasts\*\*\* of epithelial cancers, including more than 95% of primary and metastatic colorectal carcinomas. PATIENTS AND METHODS: 131I-mAbF19 was administered intravenously to 17 patients with hepatic metastases from colorectal carcinoma who were scheduled for resection of localized metastases or insertion of hepatic artery catheter for regional chemotherapy. Seven to 8 days before surgery, patients received 131I-mAbF19 at three dose levels, with at least four patients entered at each level. RESULTS: No toxicity associated with intravenous 131I-mAbF19 administration was observed. Tumor

images were obtained on planar and single-photon emission tomography (SPECT) scans in 15 of 17 patients with hepatic metastases, tumor-infiltrated portal lymph nodes, and/or recurrent pelvic disease. The smallest lesion visualized was 1 cm in diameter. The optimal time for tumor imaging was 3 to 5 days after 131I-mAbF19 administration. The use of image registration techniques allowed precise anatomic localization of 131I-mAbF19 accumulation. Immunohistochemical analysis of biopsy tissues showed expression of FAP in the tumor stroma (but not in normal liver) in all patients studied and confirmed that the FAP-positive tumor \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* were interposed between the tumor capillaries and the malignant colon epithelial cells. At the time of surgery, tumor-to-liver ratios up to 21:1 and tumor-to-serum ratios up to 9:1 were obtained. The fraction of the injected 131I-mAbF19 dose per gram tumor (%ID/g tumor) localized to hepatic metastases at the time of surgery ranged from 0.001% to 0.016%. CONCLUSION: The FAP tumor fibroblast antigen is highly expressed in primary and metastatic colorectal carcinomas and shows limited expression in normal adult tissues. This highly selective expression pattern allows imaging of colorectal carcinoma lesions as small as 1 cm in diameter on 131I-mAbF19 scans. Because of the consistent presence of FAP in the stroma of epithelial cancers and the accessibility of FAP-positive tumor \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* to circulating monoclonal antibodies (mAbs), this study suggests possible diagnostic and therapeutic applications of humanized mAbF19 and mAbF19 \*\*\*constructs\*\*\* with novel immune and nonimmune effector functions.

L8 ANSWER 11 OF 11 MEDLINE  
AN 93204185 MEDLINE  
DN 93204185  
T1 Induction of antitumor immunity by interleukin-2 gene-transduced mouse mammary tumor cells versus transduced mammary stromal fibroblasts.  
AU Tsai S C; Gansbacher B; Tait L; Miller F R; Heppner G H  
CS Breast Cancer Program, Meyer L. Prentiss Comprehensive Cancer Center of Metropolitan Detroit, Mich. 48201.  
SO JOURNAL OF THE NATIONAL CANCER INSTITUTE,

(1993 Apr 7) 85 (7) 546-53.  
Journal code: J9J. ISSN: 0027-8874.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199306  
AB BACKGROUND: Tumor cell-targeted cytokine gene transfer has been used to generate tumor cell vaccines, but this approach is limited by the need to establish and implant live tumor cells. PURPOSE: The purpose of this study was to determine if \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* could be used as an alternative vehicle for delivery of the cytokine interleukin-2 (IL-2) into the tumor microenvironment. We attempted to establish the feasibility of (a) genetic immunotherapy in a mammary tumor system and (b) engineering \*\*\*stromal\*\*\* \*\*\*fibroblasts\*\*\* as well as tumor cells. We compared the effects of tumor cell-mediated and \*\*\*stromal\*\*\* \*\*\*fibroblast\*\*\*-mediated local IL-2 expression on the generation of antitumor immune responses. METHODS: Retroviral \*\*\*vectors\*\*\* containing a human IL-2 gene were used to transduce a mouse mammary tumor line, 4T07, and an immortalized but nontumorigenic fibroblast line established from syngeneic mammary fatpads. Expression of the IL-2 gene in transduced cells was determined by measuring IL-2 secretion, by RNA-polymerase chain reaction, and by immunohistochemistry. Groups of 5-12 BALB/c mice were injected with either 4T07 cells or various doses of IL-2-secreting 4T07 cells (4T07-IL-2); tumor growth was monitored. To test whether local IL-2 expression by transduced cells could influence the growth of unmodified tumor cells, we determined tumor development in groups of mice treated with 4T07 cells co-injected with either 4T07-IL-2 cells or IL-2-secreting fibroblasts. RESULTS: 4T07-IL-2 cells induced active immunity able to reject the immunizing tumor and to resist challenge with parental 4T07 cells on the contralateral side. Mice pretreated with 4T07-IL-2 were significantly protected compared with untreated control animals or mice pretreated with irradiated 4T07 cells. The immunity induced by 4T07-IL-2 cells did not protect against challenge with another subline, 4T1, which was derived from the same

spontaneously arising mammary tumor as 4T07. Co-injection of 4T07 cells with 4T07-IL-2 cells reduced tumorigenicity, whereas co-injection of 4T07 cells with IL-2 secreting fibroblasts did not. CONCLUSION: Our results suggest that induction of anti-tumor immune response by local IL-2 production is most effective when the helper cytokine is secreted by the tumor cell. IMPLICATION: Our studies caution against the use of IL-2 gene-transduced syngeneic stromal cells as an alternative strategy of gene therapy for cancer. However, they may allow study of the mechanisms of tumor antigen recognition and the possible involvement of co-stimulatory signals for effective tumor vaccination by gene-modified cells.

=> s obesity gene or obesity protein or ob gene/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
48252 OBESITY  
418026 GENE  
40 OBESITY GENE  
(OBESITY(W)GENE)  
48252 OBESITY  
844860 PROTEIN  
1 OBESITY PROTEIN  
(OBESITY(W)PROTEIN)  
0 OB GENE/AB  
15120 OB/BI  
418026 GENE/BI  
363 OB GENE/BI  
(OB(W)GENE/BI)  
L9 398 OBESITY GENE OR OBESITY PROTEIN OR OB GENE/AB,BI

=> s l9(10a)(construct or vector)/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
0 CONSTRUCT/AB  
18002 CONSTRUCT/BI  
0 VECTOR/AB  
32375 VECTOR/BI

L10 1 L9(10a)(CONSTRUCT OR VECTOR)/AB,BI  
=> d

L10 ANSWER 1 OF 1 MEDLINE  
AN 96149401 MEDLINE  
DN 96149401  
T1 Transcriptional activation of the mouse obese (ob) gene by CCAAT/enhancer binding protein alpha.  
AU Hwang C S; Mandrup S; MacDougald O A; Geiman D E; Lane M D  
CS Department of Biological Chemistry, Johns Hopkins University

School of Medicine, Baltimore, MD 21205, USA.  
 SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Jan 23) 93 (2) 873-7.  
 Journal code: PV3 ISSN: 0027-8424.  
 CY United States  
 DT Journal, Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 OS GENBANK-S81087  
 EM 199605

=> d ab

L10 ANSWER 1 OF 1 MEDLINE  
 AB Like other adipocyte genes that are transcriptionally activated by CCAAT/enhancer binding protein alpha (C/EBP alpha) during preadipocyte differentiation, expression of the mouse obese (ob) gene is preceded by the expression of C/EBP alpha. While the 5' flanking region of the mouse ob gene contains several consensus C/EBP binding sites, only one of these sites appears to be functional. DNase I cleavage inhibition patterns (footprinting) of the ob gene promoter revealed that recombinant C/EBP alpha, as well as a nuclear factor present in fully differentiated 3T3-L1 adipocytes, but present at a much lower level in preadipocytes, protects the same region between nucleotides -58 and -42 relative to the transcriptional start site. Electrophoretic mobility-shift analysis using nuclear extracts from adipose tissue or 3T3-L1 adipocytes and an oligonucleotide probe corresponding to a consensus C/EBP binding site at nucleotides -55 to -47 generated a specific protein-oligonucleotide complex that was supershifted by antibody against C/EBP alpha. Probes corresponding to two upstream consensus C/EBP binding sites generate protein-oligonucleotide complexes. Cotransfection of a C/EBP alpha expression \*\*\*vector\*\*\* into 3T3-L1 cells with a series of 5' truncated \*\*\*ob\*\*\* promoter constructs activated reporter gene expression with all constructs containing the proximal C/EBP binding site (nucleotides -55 to -47). Mutation of this site blocked transactivation by C/EBP alpha. Taken together, these findings implicate C/EBP alpha as a transcriptional activator of the ob gene promoter

and identify the functional C/EBP binding site in the promoter.

=> s ob gene and (mesenchymal or marrow stroma# or stromal fibroblast#)/ab,bi  
 'AB' IS NOT A VALID FIELD CODE  
 15120 OB  
 418026 GENE  
 363 OB GENE  
 (OB(W)GENE)  
 0 MESENCHYMAL/AB  
 10605 MESENCHYMAL/BI  
 0 MARROW STROMA#/AB  
 113221 MARROW/BI  
 26070 STROMA#/BI  
 1657 MARROW STROMA#/BI  
 (0MARROW(W)STROMA#/BI)  
 0 STROMAL FIBROBLAST#/AB  
 16247 STROMAL/BI  
 92189 FIBROBLAST#/BI  
 443 STROMAL FIBROBLAST#/BI  
 ((STROMAL(W)FIBROBLAST#/BI)  
 0 OB GENE AND (MESENCHYMAL OR MARROW STROMA# OR STROMAL FIBROBLAST #)/AB,BI  
 L11  
 0 OB GENE AND (MESENCHYMAL OR MARROW STROMA# OR STROMAL FIBROBLAST #)/AB,BI

=> s ltmc#  
 L12 69 LTMC#

=> s il2 and ob gene/ab,bi  
 'AB' IS NOT A VALID FIELD CODE  
 0 OB GENE/AB  
 15120 OB/BI  
 418026 GENE/BI  
 363 OB GENE/BI  
 ((OB(W)GENE)/BI)  
 0 L12 AND OB GENE/AB,BI  
 L13  
 => s il2 and obesity factor/ab,bi  
 'AB' IS NOT A VALID FIELD CODE  
 0 OBESITY FACTOR/AB  
 48252 OBESITY/BI  
 417663 FACTOR/BI  
 9 OBESITY FACTOR/BI  
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 0 L12 AND OBESITY FACTOR/AB,BI  
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 48252 OBESITY/BI  
 417663 FACTOR/BI  
 9 OBESITY FACTOR/BI  
 ((OBESITY(W)FACTOR/BI)  
 0 OBESITY FACTOR/AB,BI  
 L15

=> d j - bib ab  
 YOU HAVE REQUESTED DATA FROM 9 ANSWERS - CONTINUE? Y(N);y

L15 ANSWER 1 OF 9 MEDLINE  
 AN 1999125335 MEDLINE  
 DN 99125335  
 TI Plasma alkaline phosphatase activity in children and adolescents.  
 AU Lai S W; Liu C S; Shih H C; Lin C C  
 CS Department of Family Medicine, China Medical College Hospital, Taichung, Taiwan.  
 SO CHUNG-HUA MIN KUO HSIAO ERH KO I HSUEH HU TSA CHIH, (1998 Nov-Dec) 39 (6) 386-8.  
 Journal code: IM6 ISSN: 0001-6578.  
 CY TAIWAN: Taiwan, Province of China  
 DT Journal, Article; (JOURNAL ARTICLE)  
 LA English  
 EM 199904  
 EW 19990403  
 AB From February to June in 1996, there were 47,800 students for health examination in Taichung City, Taiwan. The population consisted of the first and fourth graders of primary schools and the first grader of junior high schools. We selected 3,452 healthy students for further study by two stage sampling. In this report, 52.5% of the students were boys, and 47.5% of the students were girls. The mean age of students was 9.9 +/- 2.4 years. Girls at age 7 and age 10 had higher activity of alkaline phosphatase than boys at the same age. The peak of alkaline phosphatase activity in girls occurred at age 10. Alkaline phosphatase activity was significantly related to weight-length index by multiple regression analysis (p < 0.05). Although clinical application as an \*\*\*obesity\*\*\* still needs further investigation, in the future it may be well to routinely check this enzyme when assessing childhood obesity.

L15 ANSWER 2 OF 9 MEDLINE  
 AN 1998386814 MEDLINE  
 DN 98386814  
 TI Evaluation of risks for postoperative pulmonary complications using a preoperative consultation system.  
 AU Tonyabe M; Yamakage M; Kawamata T; Homma Y; Kurosawa S; Sasa Y; Namiki A  
 CS Department of Anesthesiology, Sapporo Medical University School of Medicine.  
 SO MASUI JAPANESE JOURNAL OF ANESTHESIOLOGY, 1998

(1998 Jul) 47 (7) 888-93.

Journal code: KHR ISSN: 0021-4892.

CY Japan

DT Journal: Article; (JOURNAL ARTICLE)

LA Japanese

EM 199812

EW 19981201

AB We retrospectively investigated the perioperative management and

postoperative pulmonary complications of patients who had

preoperative

respiratory problems and consultations with anesthesiologists.

These

patients numbered eight hundred, 23.7% of all patients who had preoperative consultations, and 40.9% and 62.0% of the 800 had preoperative and postoperative respiratory management, respectively. Forty

eight patients (6.0%) received postoperative artificial respiration.

One

hundred and twenty four patients (15.5%) had some respiratory complications post-operatively, and 5 patients (0.7%) died mainly because of the complications. In an evaluation of these patients with the

modified

predicted risk factors of Okutsu including the \*\*\*obesity\*\*\*

\*\*\*factor\*\*\* and smoking history, there was no respiratory

complication

in patients under 14 points. Patients with high points of more than

20

included almost all of the patients (114 patients, 91.9%) who had postoperative respiratory complications. We conclude that our

preoperative

consultation system works well and that the modified predicted-risk

factors for postoperative pulmonary complications is useful for the

standardization and objectivity of preoperative patient evaluation.

L15 ANSWER 3 OF 9 MEDLINE

AN 1998295690 MEDLINE

DN 98295690

TI Hyperleptinemia as a component of a metabolic syndrome of

cardiovascular

risk.

AU Leyva F; Goddard I F; Ghatei M; Proudler A J; Aldis S; Walton

C; Bloom S;

Stevenson J C

CS Wynn Department of Metabolic Medicine, Imperial College

School of Medicine

at the National Heart and Lung Institute, London, UK.

f.leyva@imperial.ac.uk

SO ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR

BIOLOGY, (1998 Jun) 18 (6)

928-33.

Journal code: B89 ISSN: 1079-5642.

CY United States

DT Journal: Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199809

EW 19980902

AB In humans, production of the adipocyte-derived peptide leptin has been

linked to adiposity, insulin, and insulin sensitivity. We therefore

considered that alterations in plasma leptin concentrations could

constitute an additional component of a metabolic syndrome of

cardiovascular risk. To explore this hypothesis, we employed factor

analysis, a multivariate statistical technique that allows reduction of

large numbers of highly intercorrelated variables to composite,

biologically meaningful factors. Seventy-four men [age, 48.4 +/- 1.3

years

(mean +/- SEM); body mass index (BMI), 25.6 +/- 0.3 kg/m<sup>2</sup>] who

were free of

coronary heart disease and diabetes underwent anthropometric

measurements

(subscapular-to-triceps [S:T] and subscapular-to-biceps [S:B]

skinfold

thickness ratios, measurement of fasting plasma leptin, and an

intravenous

glucose tolerance test (IVGTT) for assessment of insulin

sensitivity

Plasma leptin concentrations were correlated with BMI ( $r=0.57$ ,

$P<0.001$ ).

S:T ( $r=0.34$ ,  $P=0.003$ ), S:B ( $r=0.37$ ,  $P<0.001$ ), systolic and

diastolic blood

pressures (both  $r=0.24$ ,  $P=0.044$ ), fasting triglycerides ( $r=0.31$ ,

$P=0.007$ ),

serum uric acid ( $r=0.35$ ,  $P=0.003$ ), fasting glucose ( $r=0.32$ ,

$P=0.003$ ) and

insulin ( $r=0.33$ ,  $P=0.004$ ), and IVGTT insulin ( $r=0.63$ ,  $P<0.001$ ). A

negative

correlation was observed between leptin and insulin sensitivity

( $r=-0.32$ ,

$P=0.006$ ). No significant correlations emerged between plasma

leptin

concentrations and age, high density lipoprotein cholesterol, or

IVGTT

glucose. In multivariate regression analyses, BMI (standardized

coefficient [SC]=0.40,  $P<0.001$ ), fasting insulin (SC=0.23,

$P=0.036$ ), and

IVGTT insulin (SC=0.51,  $P<0.001$ ) emerged as independent

predictors of

plasma leptin concentrations ( $R^2=0.56$ ,  $P<0.001$ ). After adjustment

for BMI,

only IVGTT insulin emerged as a significant predictor of plasma

leptin

concentrations (SC=0.56,  $P<0.001$ ,  $R^2=0.45$ ,  $P<0.001$ ). Factor

analysis of

plasma leptin concentrations and the variables that are considered

relevant to the insulin resistance syndrome revealed a clustering of

plasma leptin concentrations with a factor dominated by insulin

resistance

and high IVGTT insulin, separate from a high IVGTT

glucose/central

\*\*\*obesity\*\*\* \*\*\*factor\*\*\* and a high triglyceride/low high

density

lipoprotein cholesterol factor. Together, these factors accounted for 55.9% of the total variance in the dataset. In conclusion,

interindividual

variations in plasma leptin concentrations are strongly related to the

principal components of the insulin resistance syndrome. Further

studies

are needed to determine whether the insulin-leptin axis plays a

coordinating role in this syndrome and whether plasma leptin

concentrations could provide an additional measure of

cardiovascular risk.

L15 ANSWER 4 OF 9 MEDLINE

AN 1998097582 MEDLINE

DN 98097582

TI Plasma leptin levels are increased in survivors of acute sepsis:

associated loss of diurnal rhythm, in cortisol and leptin secretion.

AU Bornstein S R; Licinio J; Tauchnitz R; Engelmann L; Negrao A

B; Gold P;

Chrousos G P

CS Developmental Endocrinology Branch, NICHD, NIMH,

Bethesda, MD 20892, USA.

SO JOURNAL OF CLINICAL ENDOCRINOLOGY AND

METABOLISM, (1998 Jan) 83 (1) 280-3.

Journal code: HRB ISSN: 0021-972X.

CY United States

DT Journal: Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer

Journals

EM 199804

EW 19980402

AB Recent animal and human studies have suggested that leptin

secretion is

closely linked to the functions of the hypothalamic-pituitary-adrenal

(HPA) axis and the immune system, both of which are crucial in

influencing

the course and outcome of critical illness. Therefore, we measured

basal

plasma leptin levels and examined the circadian secretion of leptin,

in

parallel with the hormones of the HPA axis and a key cytokine,

interleukin-6, in critically ill patients with acute sepsis. Sixteen

critically ill patients from the University of Leipzig Intensive Care

Unit

were recruited for this study. All of these patients fulfilled the

standard diagnostic criteria for sepsis. Plasma leptin levels were

measured in all patients and controls at 09:00. In addition, in a

subgroup

of eight critically ill patients and all of the nine controls plasma

leptin, cortisol, ACTH and interleukin-6 concentrations were

measured

every 4 hours for 24 hours. Mean plasma leptin levels were

three-fold

higher (18.9 +/- 4.5 ng/ml) in critically ill patients than controls (3.8

+/- 1.0 ng/ml,  $p<0.05$ ). Similarly, ACTH levels were lower (7.8

+/- 3.4

pmol/l) in patients than in controls (17.1 +/- 1.5 pmol/l,  $p<.001$ ).

- while plasma cortisol levels were increased ( $947.6 \pm 144$  nmol/l) in patients compared to controls ( $361.1 \pm 29$ ,  $p < 0.001$ ). Morning plasma interleukin-6 levels were markedly elevated in all patients with sepsis ( $1238.0 \pm 543.1$  pg/ml) versus controls ( $6.4 \pm 1.7$ ,  $p < 0.001$ ). The controls exhibited a nyctohemeral fluctuation in plasma leptin levels with peak levels at 23:00; in contrast, septic patients, had no nocturnal rise of leptin. In healthy controls, plasma leptin and cortisol had reciprocal circadian rhythms with high nocturnal leptin levels and low nocturnal cortisol concentrations; in critically ill patients, this relation was abolished. Mean leptin levels were three-fold higher in patients who survived the septic episode ( $25.5 \pm 6.2$ ,  $n = 10$ ) than in non-survivors ( $8.0 \pm 3.7$ ,  $n = 6$ ,  $p < 0.01$ ). We conclude that in addition to its function as an anti- \*\*\*obesity\*\*\* , leptin may play a role in a severe stress state such as acute sepsis.
- L15 ANSWER 5 OF 9 MEDLINE  
AN 199806747 MEDLINE  
DN 9806747  
TI Ventilatory response to CO2 in patients with snoring, obstructive hypnoea and obstructive apnoea.  
AU Appelberg J; Sundstrom G  
CS Department of Clinical Physiology/Mid-Sweden Research and Development Centre, Vastermorrland County Council, Sundsvall Hospital, Sweden.  
SO CLINICAL PHYSIOLOGY, (1997 Sep) 17 (5) 497-507.  
Journal code: DKG. ISSN: 0144-5979.  
CY ENGLAND; United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199802  
EW 19980204  
AB Obstructive sleep apnoea (OSA) is caused by an obstruction of the upper airway. Sufficient sensitivity to CO2 in the respiratory centre is known to be a critical factor for adequate tone in the upper airway muscles. The hypothesis of this study is, therefore, that the ventilatory response to CO2 is reduced in patients with OSA. Twenty-six patients who suffered from snoring, 19 snoring patients with obstructive hypnoea (OH) and 33 snoring patients with obstructive apnoea (OA), were studied. The
- control group consisted of 25 subjects from a random sample with no snoring or daytime sleepiness. Tests of the hyperoxic and hypoxic ventilatory response to CO2 were performed, as well as static and dynamic spirometry. Subjects in the OA group displayed a higher hyperoxic ( $VE/F_{et}CO_{2H} = 12.6$  l min<sup>-1</sup>%) and hypoxic ( $VE/F_{et}CO_{2H} = 15.7$  l min<sup>-1</sup>%) ventilatory response to CO2 than patients with obstructive hypnoea ( $VE/F_{et}CO_{2H} = 8.6$  l min<sup>-1</sup>%,  $VE/F_{et}CO_{2H} = 15.2$  l min<sup>-1</sup>%), snorers ( $VE/F_{et}CO_{2H} = 8.4$  l min<sup>-1</sup>%,  $VE/F_{et}CO_{2H} = 12.7$  l min<sup>-1</sup>%) and non-snorers ( $VE/F_{et}CO_{2H} = 7.6$  l min<sup>-1</sup>%,  $VE/F_{et}CO_{2H} = 9.6$  l min<sup>-1</sup>%). Multiple regression analysis reveals that neck circumference, apnoea index, oxygen desaturation index, PCO2 and sex (male gender) are correlated with  $VE/F_{et}CO_{2H}$  ( $R^2 = 0.43$ ). Multiple regression analysis also reveals that ERV (expiratory reserve volume) and sex (male gender) are correlated with  $VE/F_{et}CO_{2H}$  ( $R^2 = 0.21$ ). Arguing against the hypothesis, patients with OSA displayed an increased hyperoxic and hypoxic ventilatory response to CO2. Nocturnal apnoea frequency and the \*\*\*obesity\*\*\* in OSA may have contributed to these results.
- L15 ANSWER 6 OF 9 MEDLINE  
AN 96067418 MEDLINE  
DN 96067418  
TI Hemostatic function in young subjects with central obesity: relationship with left ventricular function  
AU Licata G; Scaglione R; Avellone G; Ganguzza A; Corrao S; Arnone S; Di Chiara T  
CS Department of Internal Medicine, University of Palermo, Italy.  
SO METABOLISM: CLINICAL AND EXPERIMENTAL, (1995 Nov) 44 (11) 1417-21.  
Journal code: MUM. ISSN: 0026-0495.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199602  
AB This study was designed to evaluate coagulation and fibrinolysis activity and their relationship with left ventricular function in young obese subjects with central fat distribution. We assessed coagulation and fibrinolysis activity by evaluation of factor VII activity, fibrinogen and plasminogen, plasminogen activator inhibitor (PAI), and tissue
- plasminogen activator antigen basally (PAI) and after venous occlusion (tPA2). These measures were evaluated in young (< 40 years) obese subjects with central fat distribution ( $n = 19$ ) and in comparable lean subjects ( $n = 20$ ). Blood glucose, triglycerides, total and high-density lipoprotein (HDL) cholesterol, apolipoprotein (apo) A1 and apo B, fasting immunoreactive insulin, and lipoprotein(a) levels were also measured by current methods. Left ventricular ejection fraction (LVEF) and peak filling rate (PFR) determined by radionuclide angiography and left ventricular mass (LVM) and LVM indexed for body height (LVM/H) determined by echocardiographic study were calculated. Central obesity was evaluated by the waist to hip ratio (WHR) according to the criteria of the Italian Consensus Conference of \*\*\*Obesity\*\*\* . \*\*\*Factor\*\*\* VII ( $P < .001$ ), fibrinogen ( $P < .001$ ), plasminogen ( $P < .001$ ), PAI activity ( $P < .001$ ), tPA1 ( $P < .02$ ), fasting blood glucose ( $P < .01$ ), apo B ( $P < .02$ ), and immunoreactive insulin ( $P < .01$ ) were significantly higher in obese than in lean subjects. In contrast, HDL cholesterol ( $P < .01$ ), tPA2 ( $P < .01$ ), LVEF ( $P < .001$ ), and PFR ( $P < .02$ ) were significantly lower in obese than in lean subjects. In all subjects, WHR correlated directly with fibrinogen and inversely with tPA2; LVEF correlated inversely with tPA1. PAI and fibrinogen, and PFR correlated inversely with factor VII activity (ABSTRACT TRUNCATED AT 250 WORDS)
- L15 ANSWER 7 OF 9 MEDLINE  
AN 92076056 MEDLINE  
DN 92076056  
TI Correlation between changes in obesity from adolescence to young adulthood and family obesity--the results of cross sectional and longitudinal studies.  
AU Wada J; Ueda K  
CS Fukuoka Prefectural Dazaifu Hospital.  
SO NIPPON KOSHU EISEI ZASSHI [JAPANESE JOURNAL OF PUBLIC HEALTH], (1990 Oct) 37 (10) 837-42.  
Journal code: A9J. ISSN: 0546-1766.  
CY Japan  
DT Journal; Article; (JOURNAL ARTICLE)  
LA Japanese  
EM 199203  
AB We conducted a survey of 356 married couples and their 552 children living

in Hisayama in Fukuoka prefecture in order to investigate the correlation between changes in obesity from adolescence to young adulthood.

1. A positive correlation between couples in weight and height could be found, but its coefficient was weak ( $r = 0.12, 0.10$ ). There was no correlation between couples in BMI.

2. The correlation between parents and their children in height, weight and BMI was significantly positive ( $r = 0.18, 0.45$ ), having a coefficient greater than that of the correlation between married couples.

3. The correlation coefficient between mother and child was greater than that of the correlation coefficient between father and child.

4. The BMI of a child with either parent obese was significantly greater than that of a child with neither parent obese. Obesity appeared more frequently in children whose BMI of parent was higher.

5. A positive correlation between the BMI of young adults and that of adolescents could be found, and the average BMI of the obesity group was higher than that of the non-obesity group even in the adolescent subjects.

6. Even after considering BMI during adolescence, the familial factor had a significant relationship to the BMI of young adulthood. These results suggest that obesity in adolescence will influence obesity in young adulthood, and that the appearance of obesity strongly correlates with the familial \*\*\*obesity\*\*\* factor. In conclusion, it is very important to take preventative measures, in cooperation with the family, early in a child's adolescent years in order to avoid obesity in adulthood.

L15 ANSWER 8 OF 9 MEDLINE  
AN 88118430 MEDLINE  
DN 88118430  
TI Psychological status of morbidly obese women before gastric restriction surgery.  
AU Hafner R J; Warts J M; Rogers J  
CS Danden Research Unit, Glenside Hospital, Eastwood, South Australia.  
SO JOURNAL OF PSYCHOSOMATIC RESEARCH, (1987) 31 (5) 607-12.  
Journal code: JUV ISSN: 0022-3999  
CY ENGLAND: United Kingdom  
DT Journal, Article; (JOURNAL ARTICLE)  
LA English

FS Priority Journals  
EM 198805  
AB One hundred and eighteen of 142 morbidly obese women had gastric restriction surgery after completing self-report questionnaire measures of psychosocial adjustment as part of their preoperative psychiatric assessment. Compared with an age-matched normal population, they scored significantly higher on measures of phobic anxiety, somatization, depression, hostility, and marital dissatisfaction, the last being associated mainly with later onset \*\*\*obesity\*\*\*.

\*\*\*Factor\*\*\*  
analysis of questionnaire and weight data showed that weight was largely independent of psychological adjustment, although associations occurred when analysis was restricted to the data on married women, in which marital and self-assertion abnormalities loaded significantly on the same factor.

L15 ANSWER 9 OF 9 MEDLINE  
AN 82215497 MEDLINE  
DN 82215497  
TI Response to fibrinolytic activity and factor VIII-related antigen to stimulation with desmopressin in hyperlipoproteinemia.  
AU Brommer E J; Gevers Leuven J A; Barrett-Bergshoeff M M; Schouten J A  
SO JOURNAL OF LABORATORY AND CLINICAL MEDICINE, (1982 Jul) 100 (1) 105-14.  
Journal code: IVR ISSN: 0022-2143.

CY United States  
DT Journal, Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals, Priority Journals  
EM 198210  
AB Impairment of fibrinolysis is supposed to contribute to CVD. In hyperlipoproteinemic patients, known to be at risk for early CVD, fibrinolytic activity was measured before and after stimulation with DDAVP. A negative correlation was found between serum triglyceride levels and fibrinolytic activity, both before and after DDAVP. A subnormal activity was invariably found when serum triglyceride concentration was above 8 mmol/L. The defect can be attributed to low levels of extrinsic plasminogen activator. High cholesterol levels were not associated with impairment of fibrinolysis. Fibrinolytic activity and response to DDAVP were lowest in those patients with hypertriglyceridemia who also had a tendency to develop hyperchylomicronemia. (type V/IV). The low

fibrinolytic activity in this type of hyperlipoproteinemia cannot be explained by \*\*\*obesity\*\*\*. \*\*\*Factor\*\*\* VIII was higher than normal in most patients with hyperlipoproteinemia, the level increased after stimulation with DDAVP in every patient. This imbalance between coagulation and fibrinolysis might increase the risk of CVD.

=> s leptin/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
0 LEPTIN/AB  
1867 LEPTIN/BI  
L16 1867 LEPTIN/AB,BI  
=> s l16 and adipocyte/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
0 ADIPOCYTE/AB  
8138 ADIPOCYTE/BI  
L18 8138 ADIPOCYTE/AB,BI  
=> s l18(10a)construct or exogenous or vector/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
0 CONSTRUCT/AB  
18002 CONSTRUCT/BI  
0 EXOGENOUS/AB  
52796 EXOGENOUS/BI  
0 VECTOR/AB  
32375 VECTOR/BI  
L19 54 L18(10a)CONSTRUCT OR EXOGENOUS OR VECTOR/AB,BI  
=> s l19 and (ob gene or leptin)/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
0 OB GENE/AB  
15120 OB/BI  
418026 GENE/BI  
363 OB GENE/BI  
((OB(W)GENE/BI)  
0 LEPTIN/AB  
1867 LEPTIN/BI  
L20 1 L19 AND (OB GENE OR LEPTIN)/AB,BI  
=> d bib ab  
L20 ANSWER 1 OF 1 MEDLINE  
AN 96214975 MEDLINE  
DN 96214975  
TI Regulation of expression of ob mRNA and protein by glucocorticoids and

# cAMP

AU Sliker L J, Sloop K W, Surface P L, Knaulinas A, LaQuier F, Manetta J, Bue-Valleskey J, Stephens T W  
 CS Endocrine Research and Technology Core Divisions, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, USA  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Mar 8) 271 (10) 5301-4.  
 Journal code: HIV ISSN: 0021-9258.

CY United States  
 DT Journal Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals, Cancer Journals  
 EM 199608  
 AB Regulation of obese gene (ob) expression in ob/ob and db/db mice and in cultured rat \*\*\*adipocytes\*\*\* was examined. It has been demonstrated that \*\*\*exogenous\*\*\* human OB protein ( \*\*\*leptin\*\*\* ) reduces food intake and weight gain, as well as insulin, glucose, and corticosterone levels in ob/ob mice. In the present report we show that

that \*\*\*leptin\*\*\* treatment down-regulates endogenous adipose ob mRNA.  
 However, treatment of isolated rat adipocytes with 100 ng/ml human or murine \*\*\*leptin\*\*\* had no direct effect on expression of endogenous ob mRNA, suggesting that \*\*\*leptin\*\*\* may be able to down-regulate its own expression by an indirect, non-autocrine mechanism. Glucocorticoids increased both ob mRNA levels and secreted \*\*\*leptin\*\*\* levels in vitro. Conversely, agents that increase intracellular cAMP, such as beta-adrenergic agonists or Bt2cAMP itself, decreased ob mRNA expression and \*\*\*leptin\*\*\* secretion. Therefore, increased glucocorticoid levels and decreased sympathetic neural activity may contribute to the elevated ob mRNA expression observed in genetically obese, hyperglucocorticoid rodents. Furthermore, \*\*\*leptin\*\*\* might regulate its own expression through a feedback mechanism involving the hypothalamic pituitary axis.

=> d his

(FILE HOME) ENTERED AT 15:12:44 ON 18 OCT 1999)

FILE 'MEDLINE' ENTERED AT 15:12:49 ON 18 OCT 1999

L1 142 S STROMA#(PYEXOGENOUS GENE OR GENE CONSTRUCT OR VECTOR)/AB,BI

L2 26 S L1 AND PROMOTER#AB,BI

L3 1 S L2 AND COLLAGEN/AB,BI

L4 14675 S MESENCHYM#AB,BI

L5 64 S L47X GENE CONSTRUCT OR EXOGENOUS GENE OR VECTOR#AB,BI

L6 12 S L5 AND PROMOTER#AB,BI

L7 443 S STROMAL FIBROBLAST#AB,BI

L8 11 S L7(PX VECTOR# OR CONSTRUCT#)/AB,BI

L9 398 S OBESITY GENE OR OBESITY PROTEIN OR OB GENE/AB,BI

L10 1 S L9(10A)X CONSTRUCT OR VECTOR/AB,BI

L11 0 S OB GENE AND (MESENCHYMAL OR MARROW STROMA# OR STROMAL FIBROBL

L12 69 S L11M#

L13 0 S L12 AND OB GENE/AB,BI

L14 0 S L12 AND OBESITY FACTOR/AB,BI

L15 9 S OBESITY FACTOR/AB,BI

L16 1867 S LEPTIN/AB,BI

L17 385 S L16 AND ADIPOCYTE#AB,BI

L18 8138 S ADIPOCYTE#AB,BI

L19 54 S L18(10A)X CONSTRUCT OR EXOGENOUS OR VECTOR/AB,BI

L20 1 S L19 AND (OB GENE OR LEPTIN)/AB,BI

=> s l1 or l4

L21 14812 L1 OR L4

=> s l21 and (ob gene or leptin)/ab,bi

'AB' IS NOT A VALID FIELD CODE

0 OB GENE/AB

15120 OB/BI

418026 GENE/BI

363 OB GENE/BI

((OB(W)GENE)/BI)

0 LEPTIN/AB

1867 LEPTIN/BI

L22 0 L21 AND (OB GENE OR LEPTIN)/AB,BI

=> file medline embase biosis inpadoc caplus

COST IN U.S. DOLLARS

ENTRY SESSION

SINCE FILE TOTAL

FULL ESTIMATED COST 17.29 17.56

FILE 'MEDLINE' ENTERED AT 15:28:51 ON 18 OCT 1999

FILE 'EMBASE' ENTERED AT 15:28:51 ON 18 OCT 1999

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FILE 'INPADOC' ENTERED AT 15:28:51 ON 18 OCT 1999

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=> s l22

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

L23 2 L22

=> dup rem l23

PROCESSING COMPLETED FOR L23

L24 2 DUP REM L23 (0 DUPLICATES REMOVED)

=> d 1-bib ab

YOU HAVE REQUESTED DATA FROM 2 ANSWERS -

CONTINUE? Y(N)Y

L24 ANSWER 1 OF 2 CAPLUS COPYRIGHT 1999 ACS

AN 1997-717829 CAPLUS

DN 128:18701

TI Use of ob protein for inducing bone formation

IN Durnam, Diane M.; Kuijper, Joseph L.; Weigle, David S.; Liu, Chung C.

PA Zymogenetics, Inc, USA, University of Washington

SO PCT Int. Appl., 42 pp.

CODEN: PIXXD2

DT Patent

LA English

FANCNT 1

PATENT NO. KIND DATE APPLICATION NO.

DATE

PI WO 9739767 A1 19971030 WO 1997US6892

19970418

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN,

CU, CZ, DE,

DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR,

KZ, LC,

LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,

NO, NZ, PL, PT,

RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ,

VN, AM,

AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK,

ES, FI, FR, GB,

GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,

GA, GN,

ML, MR, NE, SN, TD, TG

CA 2251808 AA 19971030 CA 1997-2251808 19970418

AU 9728104 A1 19971112 AU 1997-28104 19970418

EP 917469 A1 19990526 EP 1997-922438 19970418

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE,

MC, PT,

IE, FI

PRAI US 1996-15647 19960419

WO 1997-US6892 19970418

AB Methods for inducing bone formation using ob protein (\*\*\*leptin\*\*\*) are disclosed. The methods can be used for treating osteoporosis, repairing fractures, dental defects, resectioning due to oncogenesis and

elongation of the growth plate/long bone. In addn., the methods can be

used for ex vivo therapy and reinfused into a mammal.

L24 ANSWER 2 OF 2 CAPLUS COPYRIGHT 1999 ACS

AN 1997-802782 CAPLUS

DN 128-73875

T1 Hepatic fibrosis, glomerulosclerosis, and a lipodystrophy-like syndrome in

PEPCK-TGF- $\beta$ 1 transgenic mice

AU Clouthier, David E.; Comerford, Sarah A.; Hammer, Robert E. CS Department of Biochemistry, Howard Hughes Medical Institute, University

Texas Southwestern Medical Center, Dallas, TX, 75235-9050, USA

SO J Clin Invest (1997), 100(11), 2697-2713

CODEN: JCINAO; ISSN: 0021-9738

PB Rockefeller University Press

DT Journal

LA English

AB Transgenic mice overexpressing a constitutively active human TGF- $\beta$ 1

under control of the rat phosphoenolpyruvate carboxylase

regulatory

sequences developed fibrosis of the liver, kidney, and adipose

tissue, and

exhibited a severe redn. in body fat. Expression of the transgene in hepatocytes resulted in increased collagen deposition, altered

lobular

organization, increased hepatocyte turnover, and in extreme cases,

hemorrhage and thrombosis. Renal expression of the transgene was

localized to the proximal tubule epithelium, and was assoc. with

tubulointerstitial fibrosis, characterized by excessive collagen

deposition and increased fibronectin and plasminogen activator

inhibitor-1

immunoreactivity. Pronounced glomerulosclerosis was evident,

and

hydronephrosis developed with low penetrance. Expression of

TGF- $\beta$ 1

in white and brown adipose tissue resulted in a lipodystrophy-like

syndrome. All white fat deposits and brown fat pads were severely

reduced

in size, and exhibited prominent fibroplasia. This redn. in white fat

was

due to impaired adipose accretion. Introduction of the transgene

into the

ob/ob background suppressed the obesity characteristic of this

mutation,

however, transgenic mutant mice developed severe hepato- and

splenomegaly.

These studies strengthen the link between TGF- $\beta$ 1 expression and

fibrotic disease, and demonstrate the potency of TGF- $\beta$ 1 in

modulating

\*\*\*mesenchymal\*\*\* cell differentiation in vivo.

=> d his

(FILE HOME' ENTERED AT 15:12:44 ON 18 OCT 1999)

FILE 'MEDLINE' ENTERED AT 15:12:49 ON 18 OCT 1999

L1 142 S STROMA#(P)EXOGENOUS GENE OR GENE

CONSTRUCT OR VECTOR)/AB,BI

L2 26 S L1 AND PROMOTER#)/AB,BI

L3 1 S L2 AND COLLAGEN/AB,BI

L4 14675 S MESENCHYM7/AB,BI

L5 64 S L4(P)GENE CONSTRUCT OR EXOGENOUS

GENE OR VECTOR#)/AB,BI

L6 12 S L5 AND PROMOTER#)/AB,BI

L7 443 S STROMAL FIBROBLAST#)/AB,BI

L8 11 S L7(P)VECTOR# OR CONSTRUCT#)/AB,BI

L9 398 S OBESITY GENE OR OBESITY PROTEIN OR OB

GENE/AB,BI

L10 1 S L9(10A)CONSTRUCT OR VECTOR/AB,BI

L11 0 S OB GENE AND (MESENCHYMAL OR MARROW

STROMA# OR STROMAL FIBROBL

L12 69 S L10C#

L13 0 S L12 AND OB GENE/AB,BI

L14 0 S L12 AND OBESITY FACTOR/AB,BI

L15 9 S OBESITY FACTOR/AB,BI

L16 1867 S LEPTIN/AB,BI

L17 385 S L16 AND ADIPOCYTE#)/AB,BI

L18 8138 S ADIPOCYTE#)/AB,BI

L19 54 S L18(10A)CONSTRUCT OR EXOGENOUS OR

VECTOR)/AB,BI

L20 1 S L19 AND (OB GENE OR LEPTIN)/AB,BI

L21 14812 S L1 OR L4

L22 0 S L21 AND (OB GENE OR LEPTIN)/AB,BI

FILE 'MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS'

ENTERED AT 15:28:51 ON 18

OCT 1999

L23 2 S L22

L24 2 DUP REM L23 (0 DUPLICATES REMOVED)

=> s obesity protein or obesity factor or obesity gene or ob gene or

leptin/ab,bi

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

L25 9655 OBESITY PROTEIN OR OBESITY FACTOR OR

OBESITY GENE OR OB GENE OR

LEPTIN/AB,BI

=> s L25 and (stroma# or mesenchymal or adipocyte#)/ab,bi

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

L26 1681 L25 AND (STROMA# OR MESENCHYMAL OR

ADIPOCYTE#)/AB,BI

=> s L25 and (construct# or vector# or exogenous)/ab,bi

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

L27 363 L25 AND (CONSTRUCT# OR VECTOR# OR

EXOGENOUS)/AB,BI

=> s L27 and (stroma# or mesenchymal or adipocyte#)/ab,bi

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

L28 79 L27 AND (STROMA# OR MESENCHYMAL OR

ADIPOCYTE#)/AB,BI

=> dup rem L28

PROCESSING COMPLETED FOR L28

L29 35 DUP REM L28 (44 DUPLICATES REMOVED)

=> d 1-bib ab

YOU HAVE REQUESTED DATA FROM 35 ANSWERS .

CONTINUE? Y(N)Y

L29 ANSWER 1 OF 35 CAPLUS COPYRIGHT 1999 ACS

AN 1999-565879 CAPLUS

DN 131:179821

T1 Isolated \*\*\*stromal\*\*\* cells for use in the treatment of

diseases of

the central nervous system

IN Prockop, Darwin J.; Stokes, David G.; Azizi, S. Ausim; Phinney,

Donald G.

PA MCP Hahnemann University, USA

SO PCT Int. Appl., 138 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN CNT 1

PATENT NO. KIND DATE APPLICATION NO.

DATE

PI WO 9943286 A2 19990902 WO 1999-US3897

19990224

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN,

CU, CZ, DE,

DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,

IS, JP,

KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,

MG, MK, MN,

MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,



SL, TJ, TM,  
TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG,  
KZ, MD, RU,  
TJ, TM  
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH,  
CY, DE, DK, ES,  
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,  
CG, CI,  
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
PRAI US 1998-28395 19980224  
AB Methods of treating a human patient having a disease, disorder or condition of the central nervous system are disclosed. The methods include obtaining a bone marrow sample from a human donor, isolating \*\*\*stromal\*\*\* cells from the bone marrow sample, and administering the isolated \*\*\*stromal\*\*\* cells to the central nervous system of the human patient, wherein the presence of the isolated \*\*\*stromal\*\*\* cells in the brain effects treatment of the disease, disorder or condition. Stromal cells which are isolated may be cultured in vitro, they may be genetically engineered to produce therapeutic compounds, and/or they may be pre-differentiated prior to administration into the central nervous system.

L29 ANSWER 2 OF 35 MEDLINE  
AN 1999162615 MEDLINE  
DN 99162615  
TI Reversing \*\*\*adipocyte\*\*\* differentiation: implications for treatment of obesity  
AU Zhou Y T; Wang Z W; Higa M; Newgard C B; Unger R H  
CS Gifford Laboratories, Center for Diabetes Research, University of Texas  
Southwestern Medical Center, Dallas, TX 75235, USA.  
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 2) 96 (5) 2391-5.  
Journal code: PV3. ISSN: 0027-8424.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199906  
EW 19990603  
AB Conventional treatment of obesity reduces fat in mature but leaves them with lipogenic enzymes capable of rapid resynthesis of fat, a likely factor in treatment failure. Adenovirus-induced hyperleptinemia in normal rats results in rapid nonketotic fat loss that persists after hyperleptinemia disappears, whereas pair-fed controls regain their weight in 2 weeks. We report here that the

hyperleptinemia depletes \*\*\*adipocyte\*\*\* fat while profoundly down-regulating lipogenic enzymes and their transcription factor, peroxisome proliferator-activated receptor (PPAR)gamma in epididymal fat; enzymes of fatty acid oxidation and their transcription factor, PPARalpha, normally low in \*\*\*adipocytes\*\*\*, are up-regulated, as are uncoupling proteins 1 and 2. This transformation of \*\*\*adipocytes\*\*\* from cells that store triglycerides to fatty acid-oxidizing cells is accompanied by loss of the \*\*\*adipocyte\*\*\* markers, \*\*\*adipocyte\*\*\* fatty acid-binding protein 2, tumor necrosis factor alpha, and \*\*\*leptin\*\*\*, and by the appearance of the preadipocyte marker Pref-1. These findings suggest a strategy for the treatment of obesity by alteration of the \*\*\*adipocyte\*\*\* phenotype.

L29 ANSWER 3 OF 35 MEDLINE DUPLICATE  
1  
AN 1999195492 MEDLINE  
DN 99195492  
TI Transcriptional regulation of fatty acid synthase gene by insulin/glucose, polyunsaturated fatty acid and \*\*\*leptin\*\*\* in hepatocytes and \*\*\*adipocytes\*\*\* in normal and genetically obese rats.  
AU Fukuda H, Iritani N; Sugimoto T, Ikeda H  
CS Tezukayama Gakuin College, Sakai, Osaka, Japan.  
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1999 Mar) 260 (2) 505-11.  
Journal code: EMZ. ISSN: 0014-2956.  
CY GERMANY; Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199907  
EW 19990701  
AB Transcriptional regulation of the fatty acid synthase (FAS) gene by insulin/glucose, polyunsaturated fatty acids and \*\*\*leptin\*\*\* was investigated in hepatocytes and \*\*\*adipocytes\*\*\* of Wistar fatty rats and their lean littermates. The sequence spanning nucleotides -57 to -35 of FAS gene, which is responsive to insulin/glucose stimulation [Fukuda, H, Iritani, N. & Noguchi, T. (1997) FEBS Lett 406: 243-248], was linked to a reporter gene containing a heterologous promoter and transfected into rat hepatocytes or \*\*\*adipocytes\*\*\*. The activity of the reporter, chloramphenicol acetyltransferase, in the presence of glucose alone

was similar in the primary cultured cells from the lean and obese rats. In the presence of insulin/glucose, however, chloramphenicol acetyltransferase activity was markedly increased in hepatocytes of lean rats, but was not significantly increased in those of obese rats. The stimulation by insulin/glucose was reduced in arachidonic acid-treated cells of lean rats. Similarly, the stimulation by insulin/glucose was reduced in \*\*\*leptin\*\*\*-treated cells and in cells from lean rats containing an expression \*\*\*vector\*\*\* encoding \*\*\*leptin\*\*\*. However, neither polyunsaturated fatty acids nor \*\*\*leptin\*\*\*-treated cells from obese rats responded to insulin-stimulation. The same effects were observed at endogenous FAS mRNA and enzyme levels. Similar results were seen in \*\*\*adipocytes\*\*\*, although the stimulation and suppression were much smaller than in hepatocytes. The insulin-binding capacities of the receptors of liver and adipose tissue were reduced in the presence of \*\*\*leptin\*\*\* or polyunsaturated fatty acids. \*\*\*Leptin\*\*\* and polyunsaturated fatty acids appeared to suppress the insulin stimulation of FAS transcription by reducing the insulin-binding capacities of receptors. \*\*\*Leptin\*\*\* converged on the insulin/glucose response element of FAS gene and suppressed the transcription.

L29 ANSWER 4 OF 35 EMBASE COPYRIGHT 1999 ELSEVIER SCI B.V.  
AN 1999303784 EMBASE  
TI Regulation of ATP citrate-lyase gene expression in hepatocytes and \*\*\*adipocytes\*\*\* in normal and genetically obese rats.  
AU Fukuda H; Iritani N.  
CS N. Iritani, Tezukayama Gakuin College, 4-2-2 Harumidai, Sakai, Osaka 590-0113, Japan  
SO Journal of Biochemistry, (1999) 126/2 (437-444).  
Refs: 41  
ISSN: 0021-924X CODEN: JOBIAO  
CY Japan  
DT Journal; Article  
FS 029 Clinical Biochemistry  
LA English  
SL English  
AB Transcriptional regulation of ATP citrate-lyase (ACL, one of the lipogenic enzymes) gene by glucose/insulin, polyunsaturated fatty acid (PUFA), and \*\*\*leptin\*\*\* has been investigated in hepatocytes and

\*\*\*adipocytes\*\*\*  
of obese Wistar fatty rats and their lean littermates. The sequence spanning nucleotides -64 to -41 of the ACL gene, which is responsive to glucose/insulin stimulation, was linked to a reporter gene and transfected into rat hepatocytes or \*\*\*adipocytes\*\*\*. The chloramphenicol acetyltransferase (CAT) activities in the presence of glucose alone were similar in primary cultured cells from both obese and lean rats. In the presence of glucose/insulin, however, the CAT activities were markedly increased in the hepatocytes of lean rats, but were not significantly increased in those of obese rats. The stimulation by glucose/insulin was reduced in PUFA-treated cells of lean rats. The stimulation was also reduced in \*\*\*leptin\*\*\*-treated cells or \*\*\*ob\*\*\*  
\*\*\*gene\*\*\* expression \*\*\*vector\*\*\*-containing cells. However, PUFA- or \*\*\*leptin\*\*\*-treated cells from obese rats did not show a significant reduction in insulin stimulation. The same effects were observed at the endogenous mRNA and enzyme levels. Similar results were seen in \*\*\*adipocytes\*\*\*, although the stimulation and suppression levels were much smaller than in hepatocytes. The expression of endogenous insulin receptor in hepatocytes and \*\*\*adipocytes\*\*\* was reduced in the presence of \*\*\*leptin\*\*\* or PUFA. We previously found that insulin-binding capacities are also reduced in the presence of \*\*\*leptin\*\*\* or PUFA and are very low in obese rats in comparison with lean. Moreover, gel mobility shift assays using end-labeled ACL(-64/-41) revealed that nuclear factor(s) including Sp1 bind specifically to the sequence, and DNA-protein complex formation is reduced in the obese rats. Thus, the reductions in the insulin-stimulated ACL transcription may be ascribed in part to reductions in insulin binding to receptors and DNA-protein complex formation.

L29 ANSWER 5 OF 35 MEDLINE DUPLICATE  
2 AN 1999708214 MEDLINE  
DN 99208214  
TI Growth hormone in obesity.  
AU Saacchi M; Pincelli A I; Cavagnini F  
CS University of Milan, IRCCS Ospedale San Luca, Istituto Auxologico Italiano, Italy.  
SO INTERNATIONAL JOURNAL OF OBESITY AND

RELATED METABOLIC DISORDERS, (1999 Mar) 23 (3) 260-71. Ref: 150  
Journal code: BTX ISSN: 0307-0565.  
CY ENGLAND: United Kingdom  
DT Journal Article, (JOURNAL ARTICLE)  
General Review, (REVIEW)  
(REVIEW, ACADEMIC)  
LA English  
FS Priority Journals  
EM 199907  
EW 19990704  
AB Growth hormone (GH) secretion, either spontaneous or evoked by provocative stimuli, is markedly blunted in obesity. In fact obese patients display, compared to normal weight subjects, a reduced half-life, frequency of secretory episodes and daily production rate of the hormone. Furthermore, in these patients GH secretion is impaired in response to all traditional pharmacological stimuli acting at the hypothalamus (insulin-induced hypoglycaemia, arginine, galanin, L-dopa, clonidine, acute glucocorticoid administration) and to direct somatotrope stimulation by \*\*\*exogenous\*\*\* growth hormone releasing hormone (GHRH). Compounds thought to inhibit hypothalamic somatostatin (SRIH) release (pyridostigmine, arginine, galanin, atenolol) consistently improve, though do not normalize, the somatotropin response to GHRH in obesity. The synthetic growth hormone releasing peptides (GHRPs) GHRP-6 and hexarelin elicit in obese patients GH responses greater than those evoked by GHRH, but still lower than those observed in lean subjects. The combined administration of GHRH and GHRP-6 represents the most powerful GH releasing stimulus known in obesity, but once again it is less effective in these patients than in lean subjects. As for the peripheral limb of the GH-insulin-like growth factor I (IGF-I) axis, high free IGF-I, low IGF-binding proteins 1 (IGFBP-1) and 2 (IGFBP-2), normal or high IGFBP-3 and increased GH binding protein (GHP) circulating levels have been described in obesity. Recent evidence suggests that \*\*\*leptin\*\*\*, the product of \*\*\*adipocyte\*\*\* specific \*\*\*ob\*\*\* gene\*\*\*, exerts a stimulating effect on GH release in rodents; should the same hold true in man, the coexistence of high \*\*\*leptin\*\*\* and low GH serum levels in human obesity would fit

in well with the concept of a \*\*\*leptin\*\*\* resistance in this condition. Concerning the influence of metabolic and nutritional factors, an impaired somatotropin response to hypoglycaemia and a failure of glucose load to inhibit spontaneous and stimulated GH release are well documented in obese patients; furthermore, drugs able to block lipolysis and thus to lower serum free fatty acids (NEFA) significantly improve somatotropin secretion in obesity. Caloric restriction and weight loss are followed by the restoration of a normal spontaneous and stimulated GH release. On the whole, hypothalamic, pituitary and peripheral factors appear to be involved in the GH hyposecretion of obesity. A SRIH hypertone, a GHRH deficiency or a functional failure of the somatotrope have been proposed as contributing factors. A lack of the putative endogenous ligand for GHRP receptors is another challenging hypothesis. On the peripheral side, the elevated plasma levels of NEFA and free IGF-I may play a major role. Whatever the cause, the defect of GH secretion in obesity appears to be of secondary, probably adaptive, nature since it is completely reversed by the normalization of body weight. In spite of this, treatment with biosynthetic GH has been shown to improve the body composition and the metabolic efficacy of lean body mass in obese patients undergoing therapeutic severe caloric restriction. GH and GHRPs might therefore have a place in the therapy of obesity.

L29 ANSWER 6 OF 35 MEDLINE DUPLICATE  
3 AN 1999115205 MEDLINE  
DN 99115205  
TI \*\*\*Leptin\*\*\*'s actions on the reproductive axis: perspectives and mechanisms.  
AU Cunningham M J, Clifton D K, Steiner R A  
CS Graduate Program in Neurobiology & Behavior, University of Washington, Department of Obstetrics and Gynecology, Seattle, USA.  
SO BIOLOGY OF REPRODUCTION, (1999 Feb) 60 (2) 216-22.  
Ref: 123  
Journal code: A3W ISSN: 0006-3363.  
CY United States  
DT Journal Article, (JOURNAL ARTICLE)  
General Review, (REVIEW)  
(REVIEW, TUTORIAL)  
LA English



from  
-101 to -83 of the \*\*\*leptin\*\*\* gene is responsible for glucose/insulin stimulation of transcription, and that Sp1 is somehow involved in this regulation.

L29 ANSWER 9 OF 35 BIOSIS COPYRIGHT 1999 BIOSIS  
AN 1999-248934 BIOSIS  
DN PREV199900248934  
TI Mechanisms of TNF-alpha-induced insulin resistance.  
AU Holmisligh, G. S. (1)  
CS (1) Division of Biological Sciences and Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA, 02115 USA  
SO Experimental and Clinical Endocrinology & Diabetes, (1999)  
Vol. 107, No. 2, pp. 119-125  
ISSN: 0947-7349.  
DT Article  
LA English  
SL English  
AB There is now substantial evidence linking TNF-alpha to the presentation of insulin resistance in humans, animals and in vitro systems. We explored the relationship between TNF-alpha and insulin resistance using mice deficient for either TNF-alpha or one or both of its receptors, p55 and p75. In studies of TNF-alpha-deficient knockout mice with diet-induced obesity, obese TNF-alpha knockouts responded to an \*\*\*exogenous\*\*\* dose of insulin or glucose much more efficiently than TNF-alpha wild-type animals. This finding suggests that deletion of TNF-alpha leads to increased insulin sensitivity, ie decreased insulin resistance. In studies using genetically obese ob/ob mice, TNF-alpha receptor wild-type and p75 receptor knockout animals developed a pronounced hyperinsulinemia and transient hyperglycaemia, whereas p55 receptor and double-knockout animals did not. Moreover, in glucose and insulin tolerance tests, we found that p75 knockout animals exhibited profiles identical to those of the wild-type animals, but that p55 knockout animals and double mutants showed a mild improvement in insulin sensitivity, relative to the wild type. Since the improvement in sensitivity was slightly greater with double mutants, p55 alone cannot be responsible for TNF-alpha's promotion of insulin resistance in obese mice, despite the likelihood that it is more

important than p75. How TNF-alpha-related insulin resistance is mediated is not fully clear, although phosphorylation of serine residues on IRS-1 has previously been shown to be important. When we monitored Glut 4 expression in obese TNF-alpha wild-type and knockout mice, we found no convincing evidence that TNF-alpha mediation of the downregulation of Glut 4 mRNA expression is responsible for insulin resistance. However, we found an approximately 2-fold increase in insulin-stimulated tyrosine phosphorylation of the insulin receptor in the muscle and adipose tissue of TNF-alpha knockout mice, suggesting that insulin receptor signalling is an important target for TNF-alpha. Other possible mediators of TNF-alpha-induced insulin resistance include circulating free fatty acids (FFAs) and \*\*\*leptin\*\*\*.

L29 ANSWER 10 OF 35 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.  
AN 1999074781 EMBASE  
TI Serum \*\*\*leptin\*\*\* as an additional possible pathogenic factor in polycystic ovary syndrome.  
AU El Orabi H.; Ghaila A.A.; Khalifa A.; Mahfouz H.; El Shalkani A.; Shoteb N.  
CS Dr. A.A. Ghaila, Oncology Diagnostic Unit, Ain Shams Faculty of Medicine, Abbassia, Cairo, Egypt  
SO Clinical Biochemistry, (1999) 32/1 (71-75)  
Refs: 27  
ISSN: 0009-9120 CODEN: CLBIAS  
PUJ S 0009-9120(98)00091-5  
CY United States  
DT Journal; Article  
FS 010 Obstetrics and Gynecology  
029 Clinical Biochemistry  
LA English  
SL English  
AB Objectives: Recent data raised the possibility that high \*\*\*leptin\*\*\* levels may contribute to infertility in some women with PCOS. Design and methods: To assess changes in \*\*\*leptin\*\*\* levels and its relationship to some hormonal changes (insulin, testosterone, SHBG, FSH, LH, and prolactin) associated with PCOS in obese (n = 27) and nonobese (n = 18) patients when compared to obese and nonobese normal controls (n = 20). Results: \*\*\*Leptin\*\*\* concentration were significantly higher in

PCOS than in controls,  $p < 0.05$ , with 81% sensitivity and 50% specificity. Whereas, high serum insulin levels were found in obese and nonobese women with PCOS, high serum \*\*\*leptin\*\*\*, FAI together with reduced SHBG were found in obese rather than nonobese PCOS women. Moreover, hyperleptinemia in PCOS women was not correlated to hyperinsulinemia ( $r = -0.13$  and  $-0.4$  in obese and nonobese PCOS women, respectively). In the patient's group correlation analysis between fasting serum \*\*\*leptin\*\*\* and different studied variables showed some correlation with body mass index (BMI) only ( $r = 0.413$ ) suggesting that high \*\*\*leptin\*\*\* levels could be a characteristic of the obese PCOS. However, multiregression analysis showed that together with testosterone, \*\*\*leptin\*\*\* can successfully predict the presence or absence of PCOS. Conclusion: The potential significance of \*\*\*leptin\*\*\* for the pathophysiology of PCOS will await direct studies of the effects of \*\*\*exogenous\*\*\* \*\*\*leptin\*\*\* and/or its inhibitors on the reproductive axis of women, including those with PCOS.

L29 ANSWER 11 OF 35 CAPLUS COPYRIGHT 1999 ACS  
AN 1999-349750 CAPLUS  
DN 131:144032  
TI Study on mechanism of high-fat and sucrose diets in obesity development in rats  
AU Xue, Changrong; Zheng, Zixin; Zhang, Rongxin; Zhang, Xiaoliang; Li, Xuya; Inoue, Shuji  
CS Department of Nutrition, General Hospital of Chinese PLA, Beijing, 100853.  
Peop. Rep. China  
SO Yingyang Xuebao (1999), 21(1), 42-47  
CODEN: YYHPA4; ISSN: 0512-7955  
PB Yingyang Xuebao Bianjibu  
DT Journal  
LA Chinese  
AB To gain insight into mechanisms whereby high-fat and sucrose diets affect triglyceride metab. and induce obesity, changes in fasting plasma triglyceride levels, hepatic triglyceride secretion and clearance rate, insulin and lipoprotein lipase were obsd. in ventromedial hypothalamus (VMH)-lesioned normal rats. A high-fat diet had a potency to increase body wt. and body fat, but a high-sucrose diet only had an effect in

increasing body fat. Both diets could cause increase in plasma insulin

concn. Increased insulin level promoted enhancement in activity of lipoprotein lipase. A high-fat diet led to increase in \*\*\*exogenous\*\*\* triglyceride in blood, which was rapidly transferred into \*\*\*adipocyte\*\*\* under action of lipoprotein lipase. A high sucrose diet caused increase in insulin concn. which was a stimulation factor for hepatic prodn. of endogenous triglycerides. The endogenous triglycerides entered \*\*\*adipocyte\*\*\* under action of increased lipoprotein lipase.

Mechanisms by which high-fat and sucrose diets lead to obesity are different. The difference is that a high-fat diet induces increase in \*\*\*exogenous\*\*\* triglycerides, and a high-sucrose diet induces overprodn. of endogenous triglycerides. However, both diets have the same aspect, i.e. both diets cause hyperinsulinemia. Increased insulin level leads to enhancement of lipoprotein activity which promotes entrance of increased triglyceride into \*\*\*adipocyte\*\*\*.

L29 ANSWER 12 OF 35 CAPLUS COPYRIGHT 1999 ACS  
AN 1998:112467 CAPLUS  
DN 128:176972  
TI Human \*\*\*leptin\*\*\* receptor gene-related protein and its nucleic acids and therapeutic applications  
IN Akerblom, Ingrid E.  
PA Incyte Pharmaceuticals, Inc., USA; Akerblom, Ingrid E.  
SO PCT Int. Appl., 60 pp.  
CODEN: PIXXD2

DT Patent  
LA English  
FAN/CNT 2

PATENT NO. KIND DATE APPLICATION NO.  
DATE

PI WO 9805792 A2 19980212 WO 1997-US14191  
19970725

W: AT, BR, CA, CH, CN, DE, ES, FI, GB, IL, JP, KR, MX, NO, NZ, RU,  
SE, SG, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE,  
DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,  
CM, GA,  
GN, ML, MR, NE, SN, TD, TG

US 5789198 A 19980804 US 1996-691071 19960801  
US 5874535 A 19990223 US 1997-843370 19970415  
EP 920503 A2 19990609 EP 1997-937213 19970725

R: BE, DE, ES, FR, GB, IT, NL  
PRAI US 1996-691071 19960801  
US 1997-843370 19970415  
WO 1997-US14191 19970725

AB The present invention provides a polynucleotide which identifies and encodes a novel human \*\*\*leptin\*\*\* receptor gene-related protein (LRGRP). LRGRP shares part of its nucleic acid-coding sequences with a noncoding region of human \*\*\*leptin\*\*\* receptor cDNA and has homol. to the membrane-assoc. proteins of *Caenorhabditis elegans* ORF C30B5.2 and *Saccharomyces cerevisiae* ORF YJR044c. Portions of cDNAs unique to LRGRP were found in heart, placenta, lung, liver, skeletal muscle, kidney, pancreas, brain, pre- \*\*\*adipocyte\*\*\* cell lines both before and after differentiation, as well as in 6 hematopoietic cell lines and a cervical cancer cell line. The LRGRP gene maps to the same site and the \*\*\*leptin\*\*\* receptor on human chromosome 1p31. The genomic organization of the gene encoding LRGRP and the sequence of the exon/intron junction are provided. The invention also provides expression \*\*\*vectors\*\*\*, host cells, agonists, and antagonists. The invention also provides methods for treating metabolic, reproductive, connective tissue and neoplastic disorders.

L29 ANSWER 13 OF 35 CAPLUS COPYRIGHT 1999 ACS  
AN 1998:106005 CAPLUS  
DN 128:176963  
TI Porcine \*\*\*leptin\*\*\* protein, nucleic acid sequences coding therefor and uses thereof  
IN Bidwell, Christopher A.; Spurlock, Michael E.  
PA Purina Mills, Inc., USA; Purdue Research Foundation; Bidwell, Christopher  
A.; Spurlock, Michael E.  
SO PCT Int. Appl., 49 pp.  
CODEN: PIXXD2

DT Patent  
LA English  
FAN/CNT 1

PATENT NO. KIND DATE APPLICATION NO.  
DATE

PI WO 9804690 A1 19980205 WO 1997-US12483  
19970717

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,  
DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,  
LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,  
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US,

UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE,  
DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,  
CM, GA,  
GN, ML, MR, NE, SN, TD, TG

AU 9738028 A1 19980220 AU 1997-38028 19970717  
PRAI US 1996-692922 19960731  
WO 1997-US12483 19970717  
AB A porcine \*\*\*adipocyte\*\*\*-specific polypeptide, termed \*\*\*leptin\*\*\*, is expressed in the fat tissue of pigs. Expression may be altered in over fat pigs, or expression may be in the form of a protein of lesser biol. activity relative to that of leaner pigs. The porcine \*\*\*adipocyte\*\*\* polypeptide, DNA and RNA mols. coding therefor, methods for its prepn., and antibodies specific for the polypeptide are disclosed.

The nucleotide sequence of the porcine \*\*\*leptin\*\*\* gene comprising 5917 bp. cDNA comprising 501 bp. and the amino acid translation of the \*\*\*leptin\*\*\* coding sequences (166 amino acids including signal peptide) are provided. The gene contains 2 exons. There was 83% identity between the pig and human cDNA sequence and a 76% identity between pig and mouse cDNA sequence. Methods for detg. the susceptibility of a pig to fat deposition are based on measuring the levels of the porcine \*\*\*adipocyte\*\*\* polypeptide in a biol. fluid or tissue ext. or by measuring mRNA encoding the porcine \*\*\*adipocyte\*\*\* polypeptide in cells of the subject. Methods of evaluating an agent related to the deposition of fat in swine comprise contacting the agent with an \*\*\*adipocyte\*\*\* in vitro and measuring the amt. of the porcine \*\*\*adipocyte\*\*\* polypeptide or mRNA that is produced by the \*\*\*adipocyte\*\*\*. Methods of limiting fat deposition include administering porcine \*\*\*leptin\*\*\* or porcine \*\*\*leptin\*\*\* DNA, and methods of regulating intake include administering porcine \*\*\*leptin\*\*\*, porcine \*\*\*leptin\*\*\* DNA, or an antibody directed against porcine \*\*\*leptin\*\*\*.

L29 ANSWER 14 OF 35 CAPLUS COPYRIGHT 1999 ACS  
AN 1998:98346 CAPLUS  
DN 128:184666  
TI Bovine \*\*\*leptin\*\*\* protein, nucleic acid sequences coding therefor, and uses thereof  
IN Spurlock, Michael E.  
PA Purina Mills, Inc., USA; Spurlock, Michael E.  
SO PCT Int. Appl., 47 pp.  
CODEN: PIXXD2

DT Patent  
LA English

FAN/CMT 1  
PATENT NO. KIND DATE APPLICATION NO.  
DATE

PI WO 9804288 A1 19980205 WO 1997-US12532  
19970717

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN,  
CU, CZ, DE,  
DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP,  
KR, KZ,  
LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,  
MX, NO, NZ, PL,  
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA,  
UG, US,  
UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE,  
DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BI, CF, CG, CI,  
CM, GA,  
GN, ML, MR, NE, SN, TD, TG  
AU 9736032 A1 19980220 AU 1997-36032 19970717  
PRAI US 1996-688908 19960731  
WO 1997-US12532 19970717

AB A bovine \*\*\*adipocyte\*\*\* -specific polypeptide, termed  
\*\*\*leptin\*\*\*  
, is expressed in the fat tissue of cattle. Expression may be altered  
in  
overly fat cattle, or expression may be in the form of a protein of  
lesser  
biol. activity relative to that of leaner cattle. The bovine  
\*\*\*adipocyte\*\*\* polypeptide, DNA and RNA mols. coding  
therefor, methods  
for its prepn., and antibodies specific for the polypeptide are  
disclosed  
Methods for detg. the susceptibility of cattle to fat deposition are  
based  
on measuring the levels of the bovine \*\*\*adipocyte\*\*\*  
polypeptide in a  
biol. fluid or tissue ext. or by measuring mRNA encoding the  
bovine  
\*\*\*adipocyte\*\*\* polypeptide in cells of the subject. Methods of  
evaluating an agent related to the deposition of fat in cattle  
comprise  
contacting the agent with an \*\*\*adipocyte\*\*\* in vitro and  
measuring  
the amt. of the bovine \*\*\*adipocyte\*\*\* polypeptide or mRNA  
that is  
produced by the \*\*\*adipocyte\*\*\*. Methods of limiting fat  
deposition  
include administering \*\*\*leptin\*\*\* or \*\*\*leptin\*\*\* DNA,  
and  
methods of altering intake include administering \*\*\*leptin\*\*\*,  
\*\*\*leptin\*\*\* DNA, or an antibody directed against  
\*\*\*leptin\*\*\*.

L29 ANSWER 15 OF 35 MEDLINE DUPLICATE

AN 1998326258 MEDLINE  
DN 98326258  
TI Serum \*\*\*leptin\*\*\* levels in male marathon athletes before  
and after  
the marathon run.  
AU Leal-Cerro A; Garcia-Luna P P; Astorga R; Parejo J; Peiro R;  
Dieguez C;  
Casanueva F F  
CS Division of Endocrinology, Hospital Virgen del Rocio, Sevilla,  
Spain.  
SO JOURNAL OF CLINICAL ENDOCRINOLOGY AND  
METABOLISM, (1998 Jul) 83 (7)  
2376-9  
Journal code: HRB. ISSN: 0021-972X.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals; Cancer  
Journals  
EM 199810  
EW 19981001  
AB \*\*\*Leptin\*\*\* is a hormone produced by the  
\*\*\*adipocytes\*\*\* to  
regulate food intake and energy expenditure at the hypothalamic  
level. It  
is commonly accepted that the main determinants of \*\*\*leptin\*\*\*  
secretion are the net amount of body fat and the mean size of  
\*\*\*adipocytes\*\*\*. On the contrary, important \*\*\*vectors\*\*\*  
of energy  
flux in the organism, such as food intake and energy expended on  
exercise,  
are not thought to be regulators of that secretion. To understand  
whether  
\*\*\*leptin\*\*\* is regulated by an acute energy expenditure such as  
strenuous exercise, 29 male athletes who had trained for marathon  
running  
were studied before and after a marathon run and compared with 22  
nonobese, age-, sex-, and body mass index (BMI)-matched  
sedentary  
controls. Controls and marathon athletes showed no differences in  
BMI or  
fat-free mass. Marathon runners showed a strong reduction in total  
fat  
mass (6.2 +/- 0.4 kg; 9.1 +/- 0.5% of body fat) compared with  
controls  
(12.3 +/- 0.5 kg; 16.1 +/- 0.5% of body fat; P < 0.05). This  
difference in  
body composition was paralleled by a mean serum \*\*\*leptin\*\*\*  
level  
that in marathonians (2.9 +/- 0.2 micrograms/L) was significantly (P  
<  
0.05) reduced compared with that in controls (5.1 +/- 0.6  
micrograms/L).  
It is remarkable that the ratio of \*\*\*leptin\*\*\* per kg body fat,  
showed a very good agreement between the two groups, 0.40 +/-  
0.04

microgram/L kg for controls and 0.46 +/- 0.03 microgram/L kg for  
marathonians. In the two groups, \*\*\*leptin\*\*\* was correlated  
with both  
body weight, BMI, and fat mass (P < 0.001). The marathon  
trajectory was  
the standard 42.195 km accomplished in an average time of 3 h, 17  
min, 7  
s, with a calculated energy expenditure of over 2800 Cal. After the  
marathon run, a water imbalance occurred, with a significant  
decrease in  
body weight and an increase in serum albumin. A significant (P <  
0.05)  
reduction in \*\*\*leptin\*\*\* values was observed after the run (2.6  
+/-  
0.2 micrograms/L) compared with before (2.9 +/- 0.2  
micrograms/L), which  
was more relevant considering the relative hemoconcentration. In  
conclusion, 1) compared with sedentary subjects, \*\*\*leptin\*\*\*  
levels  
are reduced in male marathon runners in parallel with the relevant  
reduction in total body fat; 2) expressed as a ratio of \*\*\*leptin\*\*\*  
per kg body fat, no differences were observed between  
marathonians and  
controls; and 3) after an energy expenditure of 2800 Cal in the  
marathon  
run, a reduction in \*\*\*leptin\*\*\* levels occurred. Strong changes  
in  
energy expenditure may regulate serum \*\*\*leptin\*\*\* levels in  
man.

L29 ANSWER 16 OF 35 MEDLINE DUPLICATE

AN 1998283266 MEDLINE  
DN 98283266  
TI The biology of \*\*\*leptin\*\*\*: a review.  
AU Houseknecht K L; Baile C A; Matteri R L; Spurlock M E  
CS Department of Animal Sciences, Purdue University, West  
Lafayette, IN  
47907, USA.  
SO JOURNAL OF ANIMAL SCIENCE, (1998 May) 76 (5)  
1405-20. Ref: 176  
Journal code: HC7. ISSN: 0021-8812.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
LA English  
FS Priority Journals  
EM 199809  
EW 19980902  
AB \*\*\*Leptin\*\*\*, a 16-kDa protein secreted from white  
\*\*\*adipocytes\*\*\*  
, has been implicated in the regulation of food intake, energy  
expenditure, and whole-body energy balance in rodents and  
humans. The gene  
encoding \*\*\*leptin\*\*\* was identified by positional cloning and

is the mutation leading to the profound obese phenotype of the ob/ob mouse. \*\*\*Exogenous\*\*\* administration of \*\*\*leptin\*\*\* to ob/ob mice leads to a significant improvement in reproductive and endocrine status as well as reduced food intake and weight loss. The expression and secretion of \*\*\*leptin\*\*\* is highly correlated with body fat mass and \*\*\*adipocyte\*\*\* size. Cortisol and insulin are potent stimulators of \*\*\*leptin\*\*\* expression, and expression is attenuated by beta-adrenergic agonists, cAMP, and thiazolidinediones. The role of other hormones and growth factors in the regulation of \*\*\*leptin\*\*\* expression and secretion is emerging. \*\*\*Leptin\*\*\* circulates specifically bound to proteins in serum, which may regulate its half-life and biological activity. Isoforms of the \*\*\*leptin\*\*\* receptor, members of the interleukin-6 cytokine family of receptors, are found in multiple tissues, including the brain. Many of \*\*\*leptin\*\*\*'s effects on food intake and energy expenditure are thought to be mediated centrally via neurotransmitters such as neuropeptide Y. Multiple peripheral effects of \*\*\*leptin\*\*\* have also been recently described, including the regulation of insulin secretion by pancreatic beta cells and regulation of insulin action and energy metabolism in \*\*\*adipocytes\*\*\* and skeletal muscle. \*\*\*Leptin\*\*\* is thought to be a metabolic signal that regulates nutritional status effects on reproductive function. \*\*\*Leptin\*\*\* also plays a major role in hematopoiesis and in the anorexia accompanying an acute cytokine challenge. The profound effects of \*\*\*leptin\*\*\* on regulating body energy balance make it a prime candidate for drug therapies for humans and animals.

L29 ANSWER 17 OF 35 MEDLINE DUPLICATE  
8  
AN 1999093082 MEDLINE  
DN 99093082  
TI Fasting serum \*\*\*leptin\*\*\* levels in the analysis of body mass index cut-off values: are they useful for overweight screening in children and adolescents? A school population-based survey in three provinces of central Italy.  
AU Falorni A; Galmacci G; Bini V; Papi F; Molinari D; De Giorgi G; Faraoni F;

Celi F; Di Stefano G; Bertoli M G; Contessa G; Bacosi M L  
CS Clinica Pediatrica, Servizio Regionale di Diabetologia Pediatrica, Universita di Perugia, Italy.  
SO INTERNATIONAL JOURNAL OF OBESITY AND RELATED METABOLIC DISORDERS, (1998 Dec) 22 (12) 1197-208.  
Journal code: BTX. ISSN: 0307-0565.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199903  
EW 19990305  
AB OBJECTIVE: Body mass index (BMI) was determined in a population of school students from three provinces of central Italy. Fasting serum \*\*\*leptin\*\*\* concentrations were assayed in a large number of subjects from the same area, to determine their distribution as plotted against the standard deviation score (z-score) of BMI. DESIGN, SUBJECTS AND MEASUREMENTS: Height and weight were recorded from 31170 subjects (16175 male and 14995 female), aged 3-18 y, to \*\*\*construct\*\*\* BMI charts of children and adolescents from central Italy. Percentiles and z-score were calculated using the LMS method of Cole. Serum \*\*\*leptin\*\*\* concentrations were assayed in 1929 subjects (996 male and 933 female) after overnight fasting. RESULTS: BMI percentiles of central Italy were higher than those from standards of other European and USA populations. When plotted against the z-score of BMI, serum \*\*\*leptin\*\*\* values were distributed according to an exponential curve, showing a steep pattern and a wide distribution, as BMI values increased. The hypothesis of the existence of two subgroups, based on a different relation between \*\*\*leptin\*\*\* and BMI, was verified and a separation point between the two subgroups was identified using cluster analysis, discriminant analysis and a novel method developed by our group, hereafter referred to as 'regression clustering'. This method allows identification of the value of the independent variable (z-score of BMI) which can be taken as a separation point. This analysis provided the best results and indicated the following separation points: central Italy standard, z-score = 0.72 (76.4th percentile) for males and z-score = 0.69 (75.5th percentile) for females; French standard (the one suggested for a European

population by the European Childhood Obesity Group, ECOG), z-score = 1.46 (92.8th percentile) for males and z-score = 1.96 (97.5th percentile) for females. Similar but variable results were obtained when the same analysis was performed on serum \*\*\*leptin\*\*\* concentration, subdivided according to pubertal development (stage I, stage II-III, stage IV-V). CONCLUSIONS: Children and adolescents from central Italy had greater BMI percentiles when compared to other European populations. Fasting serum \*\*\*leptin\*\*\* concentrations showed a distribution pattern related to z-score, thus allowing to identification of two different subgroups. The z-scores of BMI, identified as separation points, indicated a trend to \*\*\*leptin\*\*\* production by \*\*\*adipocytes\*\*\* that could be taken as indicators of significant increases of fat mass. This study proposes criteria and a statistical approach that could be useful in the identification of BMI cut-off values when screening children and adolescents for overweight.

L29 ANSWER 18 OF 35 MEDLINE DUPLICATE  
9  
AN 1998289621 MEDLINE  
DN 98289621  
TI \*\*\*Leptin\*\*\* gene transfer into muscle increases lipolysis and oxygen consumption in white fat tissue in ob/ob mice.  
AU Marti A; Novo F J; Martinez-Anso E; Zarattegui M; Aguado M; Martinez J A  
CS Department of Physiology and Nutrition, University of Navarra, Pamplona, Spain.  
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 May 29) 246 (3) 859-62.  
Journal code: 9Y8. ISSN: 0006-291X.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199809  
EW 19980902  
AB The effects of \*\*\*leptin\*\*\* production in ob/ob mice injected with a plasmid expression \*\*\*vector\*\*\* containing mouse \*\*\*leptin\*\*\* cDNA in the tibialis anterior muscle were investigated. A significant reduction in food intake (-18%, p < 0.01) along the experimental period was found

after DNA injection, while differences in body weight gain were only significant (-41%,  $p < 0.05$ ) when determined between days 2.9 of the study. Concerning \*\*\*adipocytes\*\*\* metabolism, there was a significant increase in oxygen consumption in vitro (+34%,  $p < 0.05$ ) and in basal lipolysis (+151%,  $p < 0.05$ ) in DNA-injected mice compared to PBS-injected animals. Our results confirm that functional \*\*\*leptin\*\*\* can be produced in muscle and released into the blood stream and give new support to the fact that \*\*\*leptin\*\*\* may have direct auto- or paracrine effects on \*\*\*adipocytes\*\*\*, possibly contributing to the weight- and fat-reducing effects of \*\*\*leptin\*\*\* in ob/ob mice.

L29 ANSWER 19 OF 35 MEDLINE  
 AN 1999072323 MEDLINE  
 DN 99072323

TI Functional analysis of the C(-188)A polymorphism of the human \*\*\*leptin\*\*\* promoter.  
 AU Oksanen L, Palvimo J J; Jarne O A; Komula K  
 CS Department of Medicine, Institute of Biomedicine, University of Helsinki, Finland.  
 SO HUMAN GENETICS. (1998 Oct) 103 (4) 527-8.  
 Journal code: GED ISSN: 0340-6717.  
 CY GERMANY; Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199902  
 EW 19990204  
 AB Mutational analysis of the promoter region of the \*\*\*leptin\*\*\* gene in morbidly obese Finnish subjects had revealed a previously unidentified C(-188)A polymorphism in the proximal promoter that showed a weak association with elevated serum \*\*\*leptin\*\*\* levels in obese male carriers of the variant (-188A) allele. In this study we demonstrated that neither expression of reporter gene \*\*\*constructs\*\*\* driven by wild-type (-188C) or variant (-188A) proximal promoter regions, nor assay of binding of cellular proteins reveal a genotype-related difference in promoter activity.

L29 ANSWER 20 OF 35 CAPLUS COPYRIGHT 1999 ACS  
 AN 1998:86832 CAPLUS  
 DN 128-213111

TI Treatment with CL 316,243, a beta 3-adrenoceptor agonist, reduces serum

\*\*\*leptin\*\*\* in rats with diet- or aging-associated obesity, but not in Zucker rats with genetic (fa/fa) obesity  
 AU Ghorbani M; Himms-Hagen, J.  
 CS Department of Biochemistry, University of Ottawa, Ottawa, ON, K1H 8M5, Can.  
 SO Int. J. Obes. (1998), 22(1), 63-65  
 CODEN: IJOBDP; ISSN: 0307-0565

PB Stockton Press  
 DT Journal  
 LA English

AB The effect of chronic treatment with a beta 3-adrenoceptor agonist, CL 316,243 (CL), on serum \*\*\*leptin\*\*\* concn. was assessed in rats with diet-induced obesity (DIO) or with genetic obesity (fa/fa Zucker). \*\*\*Leptin\*\*\* concn. was measured in serum of young control rats with DIO and old control or genetically obese fa/fa Zucker rats, rats with DIO and old control or genetically obese fa/fa Zucker rats, that were treated chronically with CL for 2.4 wk. Treatment with CL reduced the elevated \*\*\*leptin\*\*\* concns. in young rats with DIO and in old mildly obese control rats to the low concn. of young lean rats. It did not alter the grossly elevated concn. in fa/fa rats. This effect of CL correlated well with its previously shown ability to reduce white \*\*\*adipocyte\*\*\* size, except in fa/fa rats. In CL-treated fa/fa rats, despite redns. in body fat mass and in white \*\*\*adipocyte\*\*\* size, and despite normalization of both hyperglycemia and hyperinsulinemia, the \*\*\*leptin\*\*\* concn. did not change. The lack of change in \*\*\*leptin\*\*\* concns. in fa/fa rats, despite shrinking of white \*\*\*adipocytes\*\*\* and partial reversal of the obesity, may be due to another defect.

L29 ANSWER 21 OF 35 CAPLUS COPYRIGHT 1999 ACS  
 AN 1998:413748 CAPLUS  
 DN 129:184842

TI Partial cloning and expression of the bovine \*\*\*leptin\*\*\* gene  
 AU Ji, Shaoquan; Willis, Gawan M.; Scott, Ronald R.; Spurlock, Michael E.  
 CS Purina Mills, Inc., St. Louis, MO, USA  
 SO Anim. Biotechnol. (1998), 9(1), 1-14  
 CODEN: ANBTEN; ISSN: 1049-5398

PB Marcel Dekker, Inc.  
 DT Journal  
 LA English

AB The product of the \*\*\*leptin\*\*\* (i.e., obese) gene may be an important regulator of energy metab., adiposity, and reprodn., and is perhaps linked

to meat quality determinants such as marbling. Mol. probes were developed using polymerase chain reaction (PCR) technol. to evaluate \*\*\*leptin\*\*\* expression in adipose depots and to evaluate the tissue-dependent nature of expression reported in other species. A 438 bp fragment representing the coding region of the bovine \*\*\*leptin\*\*\* gene excluding the N-terminal secretory signal was amplified, cloned into a plasmid \*\*\*vector\*\*\* (pASK75), and expressed in E. coli. Sequence anal. of the cDNA and the corresponding polypeptide indicate that, overall, both share approx. 87% homol. with the mouse and human \*\*\*leptin\*\*\* genes and polypeptides. Amino terminal sequencing (30 amino acid residues) of the recombinant bovine \*\*\*leptin\*\*\* (rBL) protein revealed 100% homol. with mouse and human \*\*\*leptin\*\*\*. The bovine \*\*\*leptin\*\*\* gene is expressed as a 3090 nt mRNA which is detected in adipose tissue, but is not found in brain (despite the appreciable fat content and lipid metab.) or other tissues. \*\*\*Leptin\*\*\* gene expression in several adipose depots (s.c., renal, and omental) was similar ( $P = .73$ ) in finished cattle.

L29 ANSWER 22 OF 35 CAPLUS COPYRIGHT 1999 ACS  
 AN 1998:42503 CAPLUS  
 DN 128-98569

TI Adenoviral mediated gene transfer in \*\*\*adipocytes\*\*\* and related implants  
 IN Crystal, Ronald G.; Magovern, Christopher J.; Rosengart, Todd; Hoffman, Lloyd; Talmor, Mia  
 PA Cornell Research Foundation, Inc., USA; Crystal, Ronald G.; Magovern, Christopher J.; Rosengart, Todd; Hoffman, Lloyd; Talmor, Mia  
 SO PCT Int. Appl., 53 pp.  
 CODEN: PXXD2

DT Patent  
 LA English  
 FAN/CNT 1

DATE PATENT NO. KIND DATE APPLICATION NO.

PI WO 9749827 A2 19971231 WO 1997-US11229 19970626

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC,



LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW, GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BI, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG, US 5869037 A 19990209 US 1996-672461 19960626 CA 2259228 A 19971231 CA 1997-2259228 19970626 AU 9735086 A1 19980114 AU 1997-35086 19970626 EP 914459 A2 19990512 EP 1997-931464 19970626 R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE, FI PRAI US 1996-672461 19960626 WO 1997-US11229 19970626 AB The present invention provides angiogenic factor adenovirus-mediated gene transfer to \*\*\*adipocytes\*\*\* and, in particular, transfer of toxic genes as a means of reducing adiposity and transfer of genes encoding angiogenic substances to induce new blood vessel growth, as well as adipose tissue implants. The adenoviral \*\*\*vector\*\*\* is replication-deficient and contains gene regulatory sequences such as a constitutive promoter element, and a gene encoding a protein such as a toxin, angiogenic growth factor, adipsin, or an Ob or \*\*\*leptin\*\*\* protein. Suitable angiogenic growth factors are the group of endothelial cell growth factors, including VEGF121, VEGF165, or VEGF189. The method can be used to treat energy storage human diseases such as obesity, diabetes, increased body fat deposition, hyperglycemia, hyperinsulinemia, hypothermia, hypertension, hypercholesterolemia, and hyperlipidemia. Angiogenesis is stimulated following adenoviral \*\*\*vector\*\*\* transfer to and expression in \*\*\*adipocytes\*\*\*.

L29 ANSWER 23 OF 35 CAPLUS COPYRIGHT 1999 ACS  
 AN 1997:785658 CAPLUS  
 DN 128 84698  
 TI \*\*\*Leptin\*\*\* inhibits insulin binding in isolated rat \*\*\*adipocytes\*\*\*  
 AU Walder, K.; Filippis, A.; Clark, S.; Zimmet, P.; Collier, G. R.  
 CS Sch. Nutrition & Public Health, Deakin Univ., Geelong, 3217, Australia  
 SO J. Endocrinol. (1997), 155(3), R5-R7  
 CODEN: JOENAK; ISSN: 0022-0795  
 PB Journal of Endocrinology  
 DT Journal  
 LA English  
 AB \*\*\*Leptin\*\*\* is secreted from adipose tissue, and is thought

to act as a 'lipostat', signaling the body fat levels to the hypothalamus resulting in adjustments to food intake and energy expenditure to maintain body wt. homeostasis. In addn., plasma \*\*\*leptin\*\*\* concns. have been shown to be related to insulin sensitivity independent of body fat content, suggesting that the hyperleptinemia found in obesity could contribute to the insulin resistance. We investigated the effects of \*\*\*leptin\*\*\* on insulin binding by isolated \*\*\*adipocytes\*\*\*. \*\*\*Adipocytes\*\*\* isolated from Sprague-Dawley rats exhibited a dose-dependent uptake of 125-labeled insulin when incubated with various concns. of \*\*\*exogenous\*\*\* \*\*\*leptin\*\*\*. For example, addn. of 50 nM \*\*\*leptin\*\*\* reduced total insulin binding in isolated \*\*\*adipocytes\*\*\* by 19% (P<0.05). Anal. of displacement curve binding data suggested that \*\*\*leptin\*\*\* reduced maximal insulin binding in a dose-dependent manner, but had no significant effect on the affinity of insulin for its binding site. We conclude that \*\*\*leptin\*\*\* directly inhibited insulin binding by \*\*\*adipocytes\*\*\*, and the role of \*\*\*leptin\*\*\* in the development of insulin resistance in obese individuals requires further investigations.

L29 ANSWER 24 OF 35 MEDLINE DUPLICATE  
 DN 97184189 MEDLINE  
 DN 97184189  
 TI Functional antagonism between CCAAT/Enhancer binding protein-alpha and peroxisome proliferator-activated receptor-gamma on the \*\*\*leptin\*\*\* promoter.  
 AU Hollenberg A N, Susulic V S, Madura J P, Zhang B, Moller D E, Tontonoz P, Sarraf P, Spiegelman B M, Lowell B B  
 CS Division of Endocrinology, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts 02215, USA.  
 NC DK02119 (NIDDK)  
 DK49569 (NIDDK)  
 DK02354 (NIDDK)  
 +  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Feb 21) 272 (8) 5283-90.  
 Journal code: HIV. ISSN: 0021-9728.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)

LA English  
 FS Priority Journals; Cancer Journals  
 OS GENBANK-U65742  
 EM 199706  
 AB The \*\*\*ob\*\*\* \*\*\*gene\*\*\* product, \*\*\*leptin\*\*\*, is a major hormonal regulator of appetite and fat cell mass. Recent work has suggested that the antidiabetic agents, the thiazolidinediones (TZ), which are also high affinity ligands of peroxisome proliferator-activated receptor-gamma (PPARgamma), inhibit \*\*\*leptin\*\*\* expression in rodents. To examine the effects of this class of drug on the \*\*\*leptin\*\*\* gene in \*\*\*adipocytes\*\*\* we performed Northern analysis on primary rat \*\*\*adipocytes\*\*\* cultured in the presence or absence of TZ. TZ reduced \*\*\*leptin\*\*\* mRNA levels by 75%. To determine whether this effect was mediated at the transcriptional level, we isolated 6510 base pairs of 5'-flanking sequence of the \*\*\*leptin\*\*\* promoter and studied reporter \*\*\*constructs\*\*\* in primary rat \*\*\*adipocytes\*\*\* and CV-1 cells. Sequence analysis demonstrated the presence of a consensus CCAAT/enhancer binding protein (C/EBP) site between -55 and -47. Our functional analysis in transfected primary rat \*\*\*adipocytes\*\*\* demonstrates that, despite the presence of a canonical direct repeat with a 1-base-pair gap site between -3951 and -3939 as well as a consensus CCAAT/enhancer binding protein (C/EBP) site between -55 and -47. Our functional analysis in transfected primary rat \*\*\*adipocytes\*\*\* demonstrates that, despite the presence of a canonical direct repeat with a 1-base-pair gap site, TZ alone decreases reporter gene expression of \*\*\*leptin\*\*\* promoter \*\*\*constructs\*\*\* ranging from -6510 to +9 to -65 to +9. In CV-1 cells, which contain endogenous PPARgamma, TZ treatment had little effect on these \*\*\*constructs\*\*\*. However, TZ treatment did inhibit C/EBPalpha-mediated transactivation of the \*\*\*leptin\*\*\* promoter. This down-regulation of \*\*\*leptin\*\*\* reporter \*\*\*constructs\*\*\* mapped to a -65 to +9 promoter fragment which binds C/EBPalpha in gel-mobility shift assays but does not bind PPARgamma2 alone or as a heterodimer with 9-cis-retinoic acid receptor. Conversely, the promoter (-5400 to +24 base pairs) of the aP2 gene, another \*\*\*adipocyte\*\*\*-specific gene, was induced 7.3-fold by TZ. Co-transfection with C/EBPalpha minimally stimulated the aP2 promoter from basal levels but notably blocked activation by TZ. These data indicate

that PPARgamma and C/EBPalpha can functionally antagonize each other on at least two separate promoters and that this mechanism may explain the down-regulation of \*\*\*leptin\*\*\* expression by thiazolidinediones.

L29 ANSWER 25 OF 35 MEDLINE DUPLICATE

AN 97272218 MEDLINE

DN 97272218

TI Obese gene expression at in vivo levels by fat pads derived from s.c.

CM Comment in: Proc Natl Acad Sci U S A 1997 Apr

29;94(9):4242-5

AU Mandrup S, Loftus T M, MacDougald O A, Kuhajda F P, Lane

MD

CS Department of Biological Chemistry, Johns Hopkins University

School of

Medicine, Baltimore, MD 21205, USA.

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF

SCIENCES OF THE UNITED STATES OF

AMERICA, (1997 Apr 29) 94 (9) 4300-5.

Journal code: PV3. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199707

AB 3T3-F442A preadipocytes implanted s.c. into athymic mice

develop into fat

pads that are indistinguishable from normal adipose tissue.

Implanted

preadipocytes harboring a beta-galactosidase transgene gave rise to

fat

pads in which almost all \*\*\*adipocytes\*\*\* expressed

beta-galactosidase. This finding proved that the implanted

3T3-F442A

preadipocytes, rather than endogenous preadipose cells, gave rise to

the

newly developed \*adipose tissue.\* 3T3-F442A preadipocytes, when

differentiated into \*\*\*adipocytes\*\*\* in cell culture, express the

obese gene at an unexpectedly low level, i.e., <1% the level in

adipose

tissue. However, adipose tissue derived from s.c. implanted

3T3-F442A

preadipocytes expressed \*\*\*leptin\*\*\* mRNA at a level

comparable to

that in epididymal adipose tissue. These findings indicate that a

factor(s) or condition, present in the tissue context and necessary

for

maximal obese gene expression, is lacking in cell culture.

Furthermore,

\*\*\*adipocytes\*\*\* derived from the implanted cells were

hormonally

responsive in that \*\*\*leptin\*\*\* mRNA levels were up-regulated

3- to 8-fold by glucocorticoid injection into the host animal. Thus, these findings indicate that adipose-specific promoter-reporter \*\*\*constructs\*\*\*, transfected into 3T3-F442A preadipocytes, can be

tested in an in vivo context during and after development of these

cells

into adipose tissue. Furthermore, the effect of transgenes on the

adipogenic development of the implanted preadipocytes can be

assessed.

Thus, this approach offers a faster and less costly alternative to the

transgenic mouse method for assessing adipose gene function.

L29 ANSWER 26 OF 35 EMBASE COPYRIGHT 1999

ELSEVIER SCI. B. V.

AN 97054688 EMBASE

DN 1997054688

TI \*\*\*Leptin\*\*\* receptor (OB-R) signaling. Cytoplasmic domain

mutational

analysis and evidence for receptor homo-oligomerization.

AU White D W., Kuropatwinski K. K., Devos R., Baumann H.,

Tartaglia L. A.

CS H. Baumann, Dept. of Molecular/Cellular Biology, Roswell Park

Cancer

Institute, Elm and Carlton Sts., Buffalo, NY 14263, United States

SO Journal of Biological Chemistry, (1997) 272(7) (4065-4071).

Refs: 41

ISSN: 0021-9258 CODEN: JBCHA3

CY United States

DT Journal; Article

FS 029 Clinical Biochemistry

LA English

AB The \*\*\*leptin\*\*\* receptor (OB-R) mediates the weight

regulatory

effects of the \*\*\*adipocyte\*\*\* secreted hormone \*\*\*leptin\*\*\*

(OB).

Previously we have shown that the long form of OB-R, expressed

predominantly in the hypothalamus, can mediate ligand-induced

activation

of signal transducer and activator of transcription factors 1, 3, and 5

and stimulate transcription via interleukin-6 and hematopoietin

receptor

responsive gene elements. Here we report that deletion and tyrosine

substitution mutagenesis of OB-R identifies two distinct regions of

the

intracellular domain important for signaling. In addition,

granulocyte-colony stimulatory factor receptor/OB-R and

OB-R/granulocyte-

colony stimulatory factor receptor chimeras are signaling competent

and

provide evidence that aggregation of two OB-R intracellular

domains is

sufficient for ligand-induced receptor activation. However,

signaling by

full-length OB-R appears to be relatively resistant to dominant

negative

repression by signaling-incompetent OB-R, suggesting that mechanisms exist to permit signaling by the long form of OB-R even in the presence of excess naturally occurring short form of OB-R.

L29 ANSWER 27 OF 35 MEDLINE

AN 97474783 MEDLINE

DN 97474783

TI Elevated levels of SREBP-2 and cholesterol synthesis in livers of mice

homozygous for a targeted disruption of the SREBP-1 gene [see

comments]

CM Comment in: J Clin Invest 1997 Oct 15;100(8):1905-6

AU Shimano H, Shimomura I, Hammer R E, Herz J, Goldstein J L,

Brown M S,

Horton J D

CS Department of Molecular Genetics, University of Texas

Southwestern Medical

Center, Dallas, Texas 75235, USA.

NC HL-20948 (NHLBI)

SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Oct 15)

100 (8) 2115-24.

Journal code: HS7 ISSN: 0021-9738.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer

Journals

EM 199801

EW 19980104

AB The synthesis of cholesterol and its uptake from plasma LDL are

regulated

by two membrane-bound transcription factors, designated sterol

regulatory

element binding protein-1 and -2 (SREBP-1 and SREBP-2). Here,

we used the

technique of homologous recombination to generate mice with

disruptions in

the gene encoding the two isoforms of SREBP-1, termed

SREBP-1a and

SREBP-1c. Heterozygous gene-disrupted mice were phenotypically

normal, but

50-85% of the homozygous (-/-) mice died in utero at embryonic

day 11.

The surviving +/- mice appeared normal at birth and throughout life.

Their

livers expressed no functional SREBP-1. There was a 1.5-fold

upregulation

of SREBP-2 at the level of mRNA and a two- to threefold increase

in the

amount of mature SREBP-2 in liver nuclei. Previous studies

showed that

SREBP-2 is much more potent than SREBP-1c, the predominant

hepatic isoform

of SREBP-1, in activating transcription of genes encoding enzymes

of

cholesterol synthesis. Consistent with this observation, the SREBP-1  $\alpha$ - animals manifested elevated levels of mRNAs for 3-hydroxy-3-methylglutaryl coenzyme A synthase and reductase, farnesyl diphosphate synthase, and squalene synthase. Cholesterol synthesis, as measured by the incorporation of [ $^3$ H]water, was elevated threefold in livers of the  $\alpha$ - mice, and hepatic cholesterol content was increased by 50%. Fatty acid synthesis was decreased in livers of the  $\alpha$ - mice. The amount of white adipose tissue was not significantly decreased, and the levels of mRNAs for lipogenic enzymes, \*\*\*adipocyte\*\*\* lipid binding protein, lipoprotein lipase, and \*\*\*leptin\*\*\* were normal in the  $\alpha$ - mice. We conclude from these studies that SREBP-2 can replace SREBP-1 in regulating cholesterol synthesis in livers of mice and that the higher potency of SREBP-2 relative to SREBP-1c leads to excessive hepatic cholesterol synthesis in these animals.

L29 ANSWER 28 OF 35 MEDLINE DUPLICATE  
12  
AN 97344143 MEDLINE  
DN 97344143  
TI Beta-3 adrenoceptor (beta-3AR) expression in \*\*\*leptin\*\*\* treated OB/OB mice.  
AU Breslow M J, An Y, Berkowitz D E  
CS The Johns Hopkins Medical Institutions, Department of Anesthesiology/Critical Care Medicine, Baltimore, Maryland 21287-8711,  
USA. mbreslow@welchlink.welch.jhu.edu  
SO LIFE SCIENCES, (1997) 61 (1) 59-64  
Journal code: L62. ISSN: 0024-3205.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199709  
EW 19970904  
AB \*\*\*Leptin\*\*\* -deficient Ob/Ob mice are hypometabolic and have reduced fat cell expression of beta-3 adrenoceptors (ARs). To determine whether \*\*\*leptin\*\*\* repletion restores beta-3 AR number, C57BL/6J Ob/Ob mice were given \*\*\*exogenous\*\*\* \*\*\*leptin\*\*\* (5 mg/kg I.P. daily) for 21 days. \*\*\*Leptin\*\*\* administration reduced body weight from 43.1  $\pm$  3.7 to 34.1  $\pm$  3.7 g in Ob/Ob animals but had no effect on weight in

wildtype animals. Body weight increased by 12% in Ob/Ob mice receiving saline. Beta-3 AR mRNA concentrations were markedly reduced in Ob/Ob animals at baseline. \*\*\*Leptin\*\*\* increased beta-3 AR mRNA to control levels in Ob/Ob mice, but had no effect in wildtype animals. \*\*\*Adipocyte\*\*\* \*\*\*leptin\*\*\* mRNA was increased by 400% in Ob/Ob mice and did not suppress with \*\*\*exogenous\*\*\* \*\*\*leptin\*\*\* administration, suggesting no direct feedback regulation of \*\*\*leptin\*\*\* synthesis. We speculate that restoration of beta-3 AR expression by repleting \*\*\*leptin\*\*\* may be important in correcting hypometabolism in Ob/Ob animals.

L29 ANSWER 29 OF 35 MEDLINE DUPLICATE  
13  
AN 1998148986 MEDLINE  
DN 98148986  
TI \*\*\*Leptin\*\*\* inhibits insulin binding in isolated rat \*\*\*adipocytes\*\*\*  
AU Walder K, Filippis A, Clark S, Zimmet P, Collier G R  
CS School of Nutrition & Public Health, Deakin University, Geelong, Australia.  
SO JOURNAL OF ENDOCRINOLOGY, (1997 Dec) 155 (3) R5-7.  
Journal code: J11. ISSN: 0022-0795.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199805  
EW 19980502  
AB \*\*\*Leptin\*\*\* is secreted from adipose tissue, and is thought to act as a 'lipostat', signalling the body fat levels to the hypothalamus resulting in adjustments to food intake and energy expenditure to maintain body weight homeostasis. In addition, plasma \*\*\*leptin\*\*\* concentrations have been shown to be related to insulin sensitivity independent of fat content, suggesting that the hyperleptinemia found in obesity could contribute to the insulin resistance. We investigated the effects of \*\*\*leptin\*\*\* on insulin binding by isolated \*\*\*adipocytes\*\*\*  
\*\*\*Adipocytes\*\*\* isolated from Sprague-Dawley rats exhibited dose-dependent reduction in the uptake of [ $^{125}$ I]-labelled insulin when incubated with various concentrations of \*\*\*exogenous\*\*\* \*\*\*leptin\*\*\*. For example, addition of 50 nM \*\*\*leptin\*\*\*

reduced total insulin binding in isolated \*\*\*adipocytes\*\*\* by 19% (P < 0.05). Analysis of displacement curve binding data suggested that \*\*\*leptin\*\*\* reduced maximal insulin binding in a dose-dependent manner, but had no significant effect on the affinity of insulin for its binding site. We conclude that \*\*\*leptin\*\*\* directly inhibited insulin binding by \*\*\*adipocytes\*\*\*, and the role of \*\*\*leptin\*\*\* in the development of insulin resistance in obese individuals requires further investigation.  
L29 ANSWER 30 OF 35 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B. V.  
AN 97380834 EMBASE  
DN 1997380834  
TI \*\*\*Leptin\*\*\* inhibits insulin binding in isolated rat \*\*\*adipocytes\*\*\*  
AU Walder K., Filippis A.; Clark S.; Zimmet P.; Collier G.R.  
CS G.R. Collier, Sch. of Nutrition and Public Health, Deakin University, Geelong 3217, Australia  
SO Journal of Endocrinology, (1997) 155/3 (R5-R7).  
Refs: 13  
ISSN: 0022-0795 CODEN: JOENAK  
CY United Kingdom  
DT Journal; Article  
FS 003 Endocrinology  
LA English  
SL English  
AB \*\*\*Leptin\*\*\* is secreted from adipose tissue, and is thought to act as a 'lipostat', signalling the body fat levels to the hypothalamus resulting in adjustments to food intake and energy expenditure to maintain body weight homeostasis. In addition, plasma \*\*\*leptin\*\*\* concentrations have been shown to be related to insulin sensitivity independent of fat content, suggesting that the hyperleptinemia found in obesity could contribute to the insulin resistance. We investigated the effects of \*\*\*leptin\*\*\* on insulin binding by isolated \*\*\*adipocytes\*\*\*  
\*\*\*Adipocytes\*\*\* isolated from Sprague-Dawley rats exhibited a dose-dependent reduction in the uptake of [ $^{125}$ I]-labelled insulin when incubated with various concentrations of \*\*\*exogenous\*\*\* \*\*\*leptin\*\*\*. For example, addition of 150 nM \*\*\*leptin\*\*\* reduced total insulin binding in isolated \*\*\*adipocytes\*\*\* by 19% (P<0.05). Analysis of displacement curve binding data suggested that

\*\*\*leptin\*\*\*  
reduced maximal insulin binding in a dose- dependent manner, but had no significant effect on the affinity of insulin for its binding site. We conclude that \*\*\*leptin\*\*\* directly inhibited insulin binding by \*\*\*adipocytes\*\*\*, and the role of \*\*\*leptin\*\*\* in the development of insulin resistance in obese individuals requires further investigation.

L29 ANSWER 31 OF 35 CAPLUS COPYRIGHT 1999 ACS  
AN 1996-701935 CAPLUS  
DN 126:2513  
TI Anti-obesity proteins  
IN Basinski, Margaret B.; Dimarchi, Richard D.; Flora, David B.; Heath, William F., Jr.; Hoffmann, James A.; Schoner, Brigitte E.; Shields, James E.; Smiley, David L.  
PA Eli Lilly and Company, USA  
SO U.S., 12 pp. Cont.-in-part of U.S. Ser. No. 381, 247.  
CODEN: USXXAM  
DT Patent  
LA English  
FAN/CNT 10  
PATENT NO. KIND DATE APPLICATION NO.  
DATE

PI US 5569744 A 19961029 US 1995-383632 19950206  
WO 9623514 A1 19960808 WO 1996-US947 19960129  
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK  
RW KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE  
IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG  
CA 2211636 AA 19960808 CA 1996-2211656 19960129  
AU 9647660 A1 19960821 AU 1996-47660 19960129  
AU 9647659 A1 19960821 AU 1996-47659 19960129  
EP 836620 A1 19980422 EP 1996-903648 19960129  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE  
JP 11501297 T2 19990202 JP 1996-523609 19960129  
PRA1 US 1995-381247 19950131  
US 1995-381034 19950131  
US 1995-381037 19950131  
US 1995-381040 19950131  
US 1995-381041 19950131  
US 1995-381047 19950131  
US 1995-381049 19950131  
US 1995-381050 19950131

US 1995-381054 19950131  
US 1995-381057 19950131  
US 1995-381163 19950131  
US 1995-381266 19950131  
US 1995-381370 19950131  
US 1995-381451 19950131  
US 1995-381661 19950131  
US 1995-381666 19950131  
US 1995-383492 19950206  
US 1995-383632 19950206  
US 1995-383649 19950206  
US 1995-383650 19950206  
US 1995-384292 19950206  
US 1995-384492 19950206  
US 1995-384649 19950206  
WO 1996-US946 19960129  
WO 1996-US947 19960129  
AB The protein translation product of the obese (ob) mouse gene, and its amino-acid substitution analogs prepd. by recombinant DNA technol. or chem. synthesis, are provided as anti-obesity proteins which, when administered to a patient, regulate fat tissue. The protein may represent a natural anti-obesity hormone. Such agents allow patients to overcome their obesity handicap and live normal lives with much reduced risk for type II diabetes, cardiovascular disease, and cancer. The preferred daily dose is 10-100 .mu.g protein/kg. Thus, a 141-amino-acid sequence preceded by Met-Arg was obtained by gene amplification from a human fat cell library by PCR, insertion into a suitable plasmid \*\*\*vector\*\*\*, cloning, and expression in Escherichia coli K12 RV308.

L29 ANSWER 32 OF 35 CAPLUS COPYRIGHT 1999 ACS  
AN 1996-342170 CAPLUS  
DN 125:26940  
TI Gene ob/ \*\*\*leptin\*\*\* -related modulators of body weight, corresponding nucleic acids and proteins, and diagnostic and therapeutic uses thereof  
IN Friedman, Jeffery M.; Zhang, Yiyang, Proenca, Ricardo; Maffei, Margherita, Halasa, Jeffrey L.; Gajiwala, Ketan; Burley, Stephen K.  
PA Rockefeller University, USA  
SO Brit. UK Pat. Appl., 304 pp.  
CODEN: BAXXDU  
DT Patent  
LA English  
FAN/CNT 5  
PATENT NO. KIND DATE APPLICATION NO.  
DATE

PI GB 2292382 A1 19960221 GB 1995-16947 19950817

GB 2292382 B2 19970716  
US 5935810 A 19990810 US 1994-347563 19941130  
PRA1 US 1994-292345 19940817  
US 1994-347563 19941130  
US 1995-438431 19950510  
US 1995-483211 19950607  
AB Polypeptides, which modulate obesity, of ca. 167 amino acids, of human and murine origin are disclosed, together with allelic variants and fragments thereof, having identical biol. activity. There are also disclosed nucleic acid sequences which encode the polypeptides, which may be inserted into a \*\*\*vector\*\*\*, either for cloning, or for expression in a bacterial, insect, fungal (esp. yeast) plant, or mammalian, host. Oligonucleotides for use either as probes or as primers for PCR amplification are disclosed. Antibodies (either monoclonal or polyclonal) are provided. The polypeptides may be conjugated with water-sol. polymers, esp. polyethyleneglycol. The polypeptides, or antagonists (including the antibodies) thereto, may be formulated for the control of body wt. The polypeptides, optionally in combination with a second component, are of use in the treatment of diabetes, high blood pressure and high cholesterol levels. Nucleic acid sequences, encoding the polypeptides, are of use in gene therapy for modulation of body wt., while sequences, hybridizable thereto, may be formulated for the same purpose. In vitro methods of evaluation (including detection and diagnosis) of levels of the OB polypeptide, including monitoring of therapeutic treatment, are also disclosed. Mouse and human \*\*\*leptin\*\*\* cDNA and the human \*\*\*leptin\*\*\* -encoding \*\*\*ob\*\*\* \*\*\*gene\*\*\* were cloned and sequenced. The human \*\*\*ob\*\*\* \*\*\*gene\*\*\* was mapped to chromosome 7. Eight microsatellite markers in close proximity to this gene were identified. Synthetic genes for mouse and human \*\*\*leptin\*\*\* with Escherichia coli-optimized codons were prepd. and expressed in E. coli. \*\*\*Leptin\*\*\*, a hormone produced by \*\*\*adipocytes\*\*\*, was found to circulate in the blood. \*\*\*Leptin\*\*\* was absent from plasma of ob/ob mice. Daily injection of recombinant \*\*\*leptin\*\*\* dramatically reduced the body mass of ob/ob mice and significantly affected body wt. of wild-type mice.

L29 ANSWER 33 OF 35 MEDLINE  
DUPLICATE

14 AN 96214975 MEDLINE  
DN 96214975  
TI Regulation of expression of ob mRNA and protein by glucocorticoids and cAMP.  
AU Sliker L J, Sloop K W, Surface P L, Kraucunas A, LaQuier F, Manetta J,  
Bue-Valleskey J, Stephens T W  
CS Endocrine Research and Technology Core Divisions, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, USA.  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Mar 8) 271 (10) 5301-4.  
Journal code: HIV ISSN: 0021-9238.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199608  
AB Regulation of obese gene (ob) expression in ob/ob and db/db mice and in cultured rat \*\*\*adipocytes\*\*\* was examined. It has been demonstrated that \*\*\*exogenous\*\*\* human OB protein ( \*\*\*leptin\*\*\* ) reduces food intake and weight gain, as well as insulin, glucose, and corticosterone levels in ob/ob mice. In the present report we show that \*\*\*leptin\*\*\* treatment down-regulates endogenous adipose ob mRNA.  
However, treatment of isolated rat \*\*\*adipocytes\*\*\* with 100 ng/ml human or murine \*\*\*leptin\*\*\* had no direct effect on expression of endogenous ob mRNA, suggesting that \*\*\*leptin\*\*\* may be able to down-regulate its own expression by an indirect, non-autocrine mechanism.  
Glucocorticoids increased both ob mRNA levels and secreted \*\*\*leptin\*\*\* levels in vitro. Conversely, agents that increase intracellular cAMP, such as beta-adrenergic agonists or Bz2cAMP itself, decreased ob mRNA expression and \*\*\*leptin\*\*\* secretion. Therefore, increased glucocorticoid levels and decreased sympathetic neural activity may contribute to the elevated ob mRNA expression observed in genetically obese, hyperglucocorticoid rodents. Furthermore, \*\*\*leptin\*\*\* might regulate its own expression through a feedback mechanism involving the hypothalamic pituitary axis.

15 AN 96210599 MEDLINE  
DN 96210599  
TI Identification of the promoter of the mouse obese gene. AU de la Brousse F C, Shan B, Chen J L  
CS Tularik Inc., South San Francisco, CA 94080, USA.  
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Apr 30) 93 (9) 4096-101.  
Journal code: PV3 ISSN: 0027-8424.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
OS GENBANK-U52147  
EM 199609  
AB Primer extension and RACE (rapid amplification of cDNA ends) assays were used to identify and sequence the 5' terminus of mouse ob mRNA.  
This sequence was used to obtain a recombinant bacteriophage containing the first exon of the encoding gene. DNA sequence analysis of the region immediately upstream of the first exon of the mouse \*\*\*ob\*\*\* revealed DNA sequences corresponding to cis-regulatory elements. A canonical TATA box was observed 30-34 base pairs upstream from the start site of transcription and a putative binding site for members of the C/EBP family of transcription factors was identified immediately upstream from the TATA box. Nuclear extracts prepared from primary \*\*\*adipocytes\*\*\* contained a DNA binding activity capable of avid and specific interaction with the putative C/EBP response element; antibodies to C/EBP alpha neutralized the DNA binding activity present in \*\*\*adipocyte\*\*\* nuclear extracts. When firefly luciferase reporter and transfected into primary \*\*\*adipocytes\*\*\*, the presumptive promoter of the mouse \*\*\*ob\*\*\* facilitated luciferase expression. When transfected into HepG2 cells, which lack C/EBP alpha, the mouse ob promoter was only weakly active. Supplementation of C/EBP alpha by cotransfection with a alpha expression \*\*\*vector\*\*\* markedly stimulated luciferase expression. Finally, an ob promoter variant mutated at the C/EBP response element was inactive in both primary \*\*\*adipocytes\*\*\* and HepG2 cells.  
These observations provide evidence for identification of a

functional promoter capable of directing expression of the mouse \*\*\*ob\*\*\*  
\*\*\*gene\*\*\*  
L29 ANSWER 35 OF 35 MEDLINE DUPLICATE  
16 AN 96149401 MEDLINE  
DN 96149401  
TI Transcriptional activation of the mouse obese ( \*\*\*ob\*\*\* ) \*\*\*gene\*\*\* by CCAAT/enhancer binding protein alpha  
AU Hwang C S, Mandrup S, MacDougald O A, Geiman D E, Lane M D  
CS Department of Biological Chemistry, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.  
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Jan 23) 93 (2) 873-7.  
Journal code: PV3 ISSN: 0027-8424.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
OS GENBANK-S81087  
EM 199605  
AB Like other \*\*\*adipocyte\*\*\* genes that are transcriptionally activated by CCAAT/enhancer binding protein alpha (C/EBP alpha) during preadipocyte differentiation, expression of the mouse obese ( \*\*\*ob\*\*\* ) \*\*\*gene\*\*\* is immediately preceded by the expression of C/EBP alpha. While the 5' flanking region of the mouse \*\*\*ob\*\*\* contains several consensus C/EBP binding sites, only one of these sites appears to be functional. DNase I cleavage inhibition patterns (footprinting) of the \*\*\*ob\*\*\* promoter revealed that recombinant C/EBP alpha, as well as a nuclear factor present in fully differentiated 3T3-L1 \*\*\*adipocytes\*\*\*, but present at a much lower level in preadipocytes, protects the same region between nucleotides -58 and -42 relative to the transcriptional start site. Electrophoretic mobility-shift analysis using nuclear extracts from adipose tissue or 3T3-L1 \*\*\*adipocytes\*\*\* and an oligonucleotide probe corresponding to a consensus C/EBP binding site at nucleotides -55 to -47 generated a specific protein-oligonucleotide complex that was supershifted by antibody against C/EBP alpha. Probes corresponding to two upstream consensus C/EBP binding sites

failed to  
generate protein-oligonucleotide complexes. Cotransfection of a  
C/EBP  
alpha expression \*\*\*vector\*\*\* into 3T3-L1 cells with a series of  
5'  
truncated \*\*\*ob\*\*\* \*\*\*gene\*\*\* promoter  
\*\*\*constructs\*\*\*  
activated reporter gene expression with all \*\*\*constructs\*\*\*  
containing the proximal C/EBP binding site (nucleotides -55 to  
-47).  
Mutation of this site blocked transactivation by C/EBP alpha.  
Taken  
together, these findings implicate C/EBP alpha as a transcriptional  
activator of the \*\*\*ob\*\*\* \*\*\*gene\*\*\* promoter and identify  
the  
functional C/EBP binding site in the promoter.

=> e prockop darwin /au  
E1 9 PROCKOP DARWIN/AU  
E2 1 PROCKOP DARWIN D/AU  
E3 547 -> PROCKOP DARWIN J/AU  
E4 6 PROCKOP DARWIN JOHNSON/AU  
E5 1 PROCKOP DARWIN JOHNSON/AU  
E6 1 PROCKOP E S/AU  
E7 21 PROCKOP L/AU  
E8 140 PROCKOP L D/AU  
E9 4 PROCKOP LEON/AU  
E10 29 PROCKOP LEON D/AU  
E11 4 PROCKOP S/AU  
E12 1 PROCKOP S A/AU

=> s e3-e4  
L30 553 ("PROCKOP DARWIN T/AU OR "PROCKOP  
DARWIN JOHNSON"/AU)

=> s L30 and (marrow stroma# or mesenchymal)/ab,bi  
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'AB' IS NOT A VALID FIELD CODE  
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L31 18 L30 AND (MARROW STROMA# OR  
MESENCHYMAL)/AB,BI

=> dup rem l31  
PROCESSING COMPLETED FOR L31  
L32 12 DUP REM L31 (6 DUPLICATES REMOVED)

=> d 1- bib ab  
YOU HAVE REQUESTED DATA FROM 12 ANSWERS -  
CONTINUE? Y(N/Y)

L32 ANSWER 1 OF 12 CAPLUS COPYRIGHT 1999 ACS  
AN 1999:565879 CAPLUS  
DN 131:179821  
TI Isolated stromal cells for use in the treatment of diseases of the  
central

nervous system  
IN \*\*\*Prockop, Darwin J\*\*\* , Stokes, David G.; Azizi, S. Austim;  
Phinney,  
Donald G.  
PA MCP Hahnemann University, USA  
SO PCT Int. Appl., 138 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN,CNT 1  
PATENT NO. KIND DATE APPLICATION NO.  
DATE  
----- --  
PJ WO 9943286 A2 19990902 WO 1999-US3897  
19990224  
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN,  
CU, CZ, DE,  
DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,  
IS, JP,  
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,  
MG, MK, MN,  
MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,  
SL, TJ, TM,  
TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG,  
KZ, MD, RU,  
TJ, TM  
RW, GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH,  
CY, DE, DK, ES,  
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,  
CG, CI,  
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
PRAI US 1998-28395 19980224  
AB Methods of treating a human patient having a disease, disorder or  
condition of the central nervous system are disclosed. The methods  
include obtaining a bone marrow sample from a human donor,  
isolating  
stromal cells from the bone marrow sample, and administering the  
isolated  
stromal cells to the central nervous system of the human patient,  
wherein  
the presence of the isolated stromal cells in the brain effects  
treatment  
of the disease, disorder or condition. Stromal cells which are  
isolated  
may be cultured in vitro, they may be genetically engineered to  
produce  
therapeutic compds. and/or they may be pre-differentiated prior to  
administration into the central nervous system.

L32 ANSWER 2 OF 12 CAPLUS COPYRIGHT 1999 ACS  
AN 1999:616004 CAPLUS  
TI \*\*\*Marrow\*\*\* \*\*\*stromal\*\*\* cells migrate throughout  
forebrain and  
cerebellum, and they differentiate into astrocytes after injection into  
neonatal mouse brains  
AU Kopen, Gene C.; \*\*\*Prockop, Darwin J.\*\*\* ; Phinney, Donald  
G.

CS Center for Gene Therapy, MCP Hahnemann University,  
Philadelphia, PA,  
19102-1192, USA  
SO Proc. Natl. Acad. Sci. U. S. A. (1999), 96(19), 10711-10716  
CODEN: PNASA6; ISSN: 0027-8424  
PB National Academy of Sciences  
DT Journal  
LA English  
AB Stem cells are a valuable resource for treating disease, but limited  
access to stem cells from tissues such as brain restricts their utility.  
Here, we injected \*\*\*narrow\*\*\* \*\*\*stromal\*\*\* cells  
(MSCs) into the  
lateral ventricle of neonatal mice and asked whether these  
multipotential  
\*\*\*mesenchymal\*\*\* progenitors from bone marrow can adopt  
neural cell  
fates when exposed to the brain microenvironment. By 12 days  
postinjection, MSCs migrated throughout the forebrain and  
cerebellum  
without disruption to the host brain architecture. Some MSCs  
within the  
striatum and the mol. layer of the hippocampus expressed glial  
fibrillary  
acidic protein and, therefore, differentiated into mature astrocytes.  
MSCs also populated neuron rich regions including the Islands of  
Calleja,  
the olfactory bulb, and the internal granular layer of the cerebellum.  
A  
large no. of MSCs also were found within the external granular  
layer of  
the cerebellum. In addn., neurofilament pos. donor cells were  
found  
within the reticular formation of the brain stem, suggesting that  
MSCs  
also may have differentiated into neurons. Therefore, MSCs are  
capable of  
producing differentiated progeny of a different dermal origin after  
implantation into neonatal mouse brains. These results suggest that  
MSCs  
are potentially useful as vectors for treating a variety of central  
nervous system disorders.

L32 ANSWER 3 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS  
DUPLICATE 1  
AN 1999:132732 BIOSIS  
DN PREV199900132732  
TI Plastic adherent stromal cells from the bone marrow of commonly  
used  
strains of inbred mice: Variation in yield, growth, and  
differentiation.  
AU Phinney, Donald G. (1); Kopen, Gene; Isaacson, Rivka L.;  
\*\*\*Prockop,\*\*\*  
\*\*\* Darwin J.\*\*\*  
CS (1) 10314 New College Build., Mainstop 421, 245 N. 15th St.,  
Philadelphia, PA 19102 USA  
SO Journal of Cellular Biochemistry, (March 15, 1999) Vol. 72, No.  
4, pp.

- 570-585.  
ISSN: 0730-2312.  
DT Article  
LA English  
AB Bone \*\*\*marrow\*\*\* \*\*\*stroma\*\*\* contains a unique cell population, referred to as \*\*\*marrow\*\*\* \*\*\*stromal\*\*\* cells (MSCs), capable of differentiating along multiple \*\*\*mesenchymal\*\*\* cell lineages.  
A standard liquid culture system has been developed to isolate MSCs from whole marrow by their adherence to plastic wherein the cells grow as clonal populations derived from a single precursor termed the colony-forming-unit fibroblast (CFU-F). Using this liquid culture system, we demonstrate that the relative abundance of MSCs in the bone marrow of five commonly used inbred strains of mice varies as much as 10-fold, and that the cells also exhibit markedly disparate levels of alkaline phosphatase expression, an early marker of osteoblast differentiation. For each strain examined, the method of isolating MSCs by plastic adherence yields a heterogeneous cell population. These plastic adherent cells also exhibit widely varying growth kinetics between the different strains.  
Importantly, of three inbred strains commonly used to prepare transgenic mice that we examined, only cells derived from FVB/N marrow readily expand in culture. Further analysis of cultures derived from FVB/N marrow showed that most plastic adherent cells express CD11b and CD45, epitopes of lymphohematopoietic cells. The latter consists of both pre-B-cell progenitors, granulocytic and monocytic precursors, and macrophages.  
However, a subpopulation of the MSCs appear to represent bona fide \*\*\*mesenchymal\*\*\* progenitors, as cells can be induced to differentiate into osteoblasts and adipocytes after exposure to dexamethasone and into myoblasts after exposure to amphoterin B. Our results point to significant strain differences in the properties of MSCs and indicate that standard methods cannot be applied to murine bone marrow to isolate relatively pure populations of MSCs.  
L32 ANSWER 4 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS  
AN 1999:159793 BIOSIS  
DN PREV199900159793
- TI Transplantability and therapeutic effects of bone marrow-derived \*\*\*mesenchymal\*\*\* cells in children with osteogenesis imperfecta.  
AU Horwitz, Edwin M. (1). \*\*\*Prockop, Darwin J.\*\*\* ; Fitzpatrick, Lorraine A.; Koo, Winston W. K.; Gordon, Patricia L. (1); Neel, Michael (1); Sussman, Michael; Orchard, Paul; Marx, Jeffrey C.; Pyritz, Reed E.; Brenner, Malcolm K. (1)  
CS (1) Cell and Gene Therapy Program, St. Jude Children's Research Hosp., 332 North Lauderdale, Memphis, TN 38105 USA  
SO Nature Medicine, (March, 1999) Vol. 5, No. 3, pp. 309-313.  
ISSN: 1078-8956.  
DT Article  
LA English  
AB In principle, transplantation of \*\*\*mesenchymal\*\*\* progenitor cells would attenuate or possibly correct genetic disorders of bone, cartilage and muscle, but clinical support for this concept is lacking. Here we describe the initial results of allogeneic bone marrow transplantation in three children with osteogenesis imperfecta, a genetic disorder in which osteoblasts produce defective type I collagen, leading to osteopenia, multiple fractures, severe bony deformities and considerably shortened stature. Three months after osteoblast engraftment (1.5-2.0% donor cells), representative specimens of trabecular bone showed histologic changes indicative of new dense bone formation. All patients had increases in total body bone mineral content ranging from 21 to 29 grams (median, 28), compared with predicted values of 0 to 4 grams (median, 0) for healthy children with similar changes in weight. These improvements were associated with increases in growth velocity and reduced frequencies of bone fracture. Thus, allogeneic bone marrow transplantation can lead to engraftment of functional \*\*\*mesenchymal\*\*\* progenitor cells, indicating the feasibility of this strategy in the treatment of osteogenesis imperfecta and perhaps other \*\*\*mesenchymal\*\*\* stem cell disorders as well.  
L32 ANSWER 5 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS  
DUPLICATE 2  
AN 1998:231716 BIOSIS  
DN PREV199800231716  
TI Engraftment and migration of human bone \*\*\*marrow\*\*\* \*\*\*stromal\*\*\* cells implanted in the brains of albino rats-similarities to astrocyte
- grfts.  
AU Azizi, S. Ausim (1); Stokes, David; Augelli, Brian J.; Digrolano, Carla; \*\*\*Prockop, Darwin J.\*\*\*  
CS (1) Dep. Neurol., Allegheny Univ. Health Sci., Broad and Vine St., MS 423, Philadelphia, PA 19102 USA  
SO Proceedings of the National Academy of Sciences of the United States of America, (March 31, 1998) Vol. 95, No. 7, pp. 3908-3913.  
ISSN: 0027-8424.  
DT Article  
LA English  
AB Neurotransplantation has been used to explore the development of the central nervous system and for repair of diseased tissue in conditions such as Parkinson's disease. Here, we examine the effects of direct injection into rat brain of human \*\*\*marrow\*\*\* cells (MSCs), a subset of cells from bone marrow that include stem-like precursors for nonhematopoietic tissues. Human MSCs isolated by adherence to plastic were infused into the corpus striatum. Five to 72 days later, brain sections were examined for the presence of the donor cells. About 20% of the infused cells had engrafted. There was no evidence of an inflammatory response or rejection. The cells had migrated from the injection site along known pathways for migration of neural stem cells to successive layers of the brain. After infusion into the brain, the human MSCs lost their immunoreactivity to antibodies for collagen I. Initially, the human cells continued to stain with antibodies to fibronectin but the region of staining with fibronectin was significantly decreased at 30 and 72 days. The results suggest that MSCs may be useful vehicles for autotransplantation in both cell and gene therapy for a variety of diseases of the central nervous system.  
L32 ANSWER 6 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS  
DUPLICATE 3  
AN 1998:132318 BIOSIS  
DN PREV199800132318  
TI \*\*\*Marrow\*\*\* \*\*\*stromal\*\*\* cells as a source of progenitor cells for nonhematopoietic tissues in transgenic mice with a phenotype of osteogenesis imperfecta.  
AU Pereira, Ruth F.; O'Hara, Michael D.; Laptev, Alexey V.; Halford, Kenneth W.; Pollard, Marek D.; Class, Reiner; Simon, Daniela; Livezey,

Kristin;

\*\*\*Prockop, Darwin J. (1)\*\*\*  
CS (1) Cent. Gene Therapy, Allegheny Univ. Health Sci., 245 N. 15 St., 10118  
NCB; Mail Stop 421, Philadelphia, PA 19102-1192 USA  
SO Proceedings of the National Academy of Sciences of the United States of America, (Feb. 3, 1998) Vol. 95, No. 3, pp. 1142-1147.  
ISSN: 0027-8424.  
DT Article  
LA English  
AB \*\*\*Marrow\*\*\* \*\*\*\*stromal\*\*\* cells from wild-type mice were infused into transgenic mice that had a phenotype of fragile bones resembling osteogenesis imperfecta because they expressed a human minigene for type I collagen. In mice that were irradiated with potentially lethal levels (700 cGy) or sublethal levels (350 cGy), DNA from the donor \*\*\*\*marrow\*\*\* \*\*\*\*stromal\*\*\* cells was detected consistently in marrow, bone, cartilage, and lung either 1 or 2.5 mo after the infusions. The DNA also was detected but less frequently in the spleen, brain, and skin. There was a small but statistically significant increase in both collagen content and mineral content of bone 1 mo after the infusion. Similar results were obtained with infusion of relatively large amounts of wild-type whole marrow cells into the transgenic mice. In experiments in which male \*\*\*\*marrow\*\*\* \*\*\*\*stromal\*\*\* cells were infused into a female osteogenesis imperfecta-transgenic mouse, fluorescence in situ hybridization assays for the Y chromosome indicated that, after 2.5 mo, donor male cells accounted for 4-19% of the fibroblasts or fibroblast-like cells obtained in primary cultures of the lung, calvaria, cartilage, long bone, tail, and skin. In a parallel experiment in which whole marrow cells from a male mouse were infused into a female immunodeficient rag-2 mouse, donor male cells accounted for 4-6% of the fibroblasts or fibroblast-like cells in primary cultures. The results support previous suggestions that \*\*\*\*marrow\*\*\* \*\*\*\*stromal\*\*\* cells or related cells in marrow serve as a source for continual renewal of cells or related cells in marrow serve as a source for continual renewal of cells in a number of nonhematopoietic tissues.

L32 ANSWER 7 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS

DUPLICATE 4  
AN 1998:267074 BIOSIS  
DN PREV199800267074  
TI What holds us together? Why do some of us fall apart? What can we do about it.  
AU \*\*\*Prockop, Darwin J. (1)\*\*\*  
CS (1) Cent. Gene Therapy, Allegheny Univ. Health Sciences, 245 N. 15th Street, Mail Stop 421, Philadelphia, PA USA  
SO Matrix Biology, (March, 1998) Vol. 16, No. 9, pp. 519-528.  
ISSN: 0945-053X.  
DT Article  
LA English  
AB One of the intriguing questions about complex organisms is, What holds them together? One of the principal answers is the tough, fibrous material known as collagen. A related question is, How is collagen made? The biosynthesis of the protein has several unusual features. One is the extensive use of the principle of spontaneous self-assembly seen in the formation of crystals. The three polypeptide chains of the protein fold into a triple-helical conformation by a process that begins with the formation of a small nucleus of triple helix at the C-terminus of the molecule and then propagation of the nucleus in a zipper-like fashion. Also, the self-assembly of the collagen monomers into fibrils is an entropy driven, crystallization-like process. Why do some of them fall apart? Mutations that alter the expression or primary structure of collagen are the predominant causes of severe skeletal defects such as osteogenesis imperfecta and chondrodysplasias. Mutations that have milder effects on the synthesis or structure of the protein are found in a subset of patients with more common diseases such as osteoporosis and early onset osteoarthritis. What can we do about the defects in collagen? Recent results have emphasized the importance of earlier observations that marrow contains a small subset of cells that are progenitors of osteoblasts, chondroblasts and several other types of nonhematopoietic cells. After systemic infusion into irradiated mice, the infused cells slowly replace a small fraction of the cells in bone, cartilage, lung and several other tissues. Therefore, the results suggest that the cells, known as \*\*\*\*mesenchymal\*\*\* stem cells or \*\*\*\*marrow\*\*\* \*\*\*\*stromal\*\*\* cells, can be used for both cell and gene therapy of diseases in which bone, cartilage and other connective tissues fall apart.

L32 ANSWER 8 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS  
AN 1999:87279 BIOSIS  
DN PREV19990087279  
TI A pvalII RFLP at the porcine orosomucoid (ORM) locus.  
AU \*\*\*Prockop, Darwin J. (1)\*\*\*  
CS (1) Cent. Gene Therapy, Allegheny Univ. Health Sciences, MCP-Hahnemann Sch. Med., 245 North 15th Street, Mail Stop 421, Philadelphia, PA 19102 USA  
SO Journal of Cellular Biochemistry Supplement, (1998) Vol. 0, No. 30-31, pp. 284-285.  
ISSN: 0733-1959.  
DT Article  
LA English  
L32 ANSWER 9 OF 12 CAPLUS COPYRIGHT 1999 ACS  
AN 1999:47340 CAPLUS  
TI \*\*\*\*Marrow\*\*\* \*\*\*\*stromal\*\*\* cells as stem cells for continual renewal of nonhematopoietic tissues and as potential vectors for gene therapy  
AU \*\*\*Prockop, Darwin J.\*\*\*  
CS Center for Gene Therapy, Allegheny Univ. Health Sci., Hahnemann Sch. Med., Philadelphia, PA, 19102, USA  
SO J. Cell. Biochem. (1998), (Suppl. 30/31), 284-285  
CODEN: JCEBD5; ISSN: 0730-2312  
PB Wiley-Liss, Inc.  
DT Journal  
LA English  
AB Unavailable  
L32 ANSWER 10 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS  
DUPLICATE 5  
AN 1997:223263 BIOSIS  
DN PREV199799514979  
TI \*\*\*\*Marrow\*\*\* \*\*\*\*stromal\*\*\* cells as stem cells for nonhematopoietic tissues.  
AU \*\*\*Prockop, Darwin J.\*\*\*  
CS Cent. Gene Therapy, Allegheny Univ. Health Sci., MCP-Hahnemann Sch. Med., 245 North 15th St., Mail Stop 421, Philadelphia, PA 19102 USA  
SO Science (Washington D C), (1997) Vol. 276, No. 5309, pp. 71-74.  
ISSN: 0036-8075.  
DT General Review  
LA English  
AB \*\*\*\*Marrow\*\*\* \*\*\*\*stromal\*\*\* cells can be isolated from other cells in marrow by their tendency to adhere to tissue culture plastic. The cells have many of the characteristics of stem cells for tissues that can roughly be defined as \*\*\*\*mesenchymal\*\*\*, because they can be differentiated in culture into osteoblasts, chondrocytes, adipocytes,



and even myoblasts. Therefore, \*\*\*marrow\*\*\* \*\*\*stromal\*\*\* cells present an intriguing model for examining the differentiation of stem cells. Also, they have several characteristics that make them potentially useful for cell and gene therapy.

L32 ANSWER 11 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS  
AN 1997-46949 BIOSIS  
DN PREV199799346152  
TI Use of \*\*\*marrow\*\*\* \*\*\*stromal\*\*\* cells to replace bone cells in a transgenic mouse model for osteogenesis imperfecta.  
AU Pereira, Ruth F. (1); Halford, Kenneth W. (1); O'Hara, Michael D.; Pollard, Marea D.; Volpe, Patricia; Laptev, Alexey (1); \*\*\*Prockop, \*\*\*  
\*\*\*Darwin J. (1)\*\*\*  
CS (1) Thomas Jefferson Univ., Dep. Biochem., Philadelphia, PA USA  
SO Matrix Biology, (1996) Vol. 15, No. 3, pp. 188.  
Meeting Info.: Sixth International Conference on the Molecular Biology and Pathology of Matrix Philadelphia, Pennsylvania, USA June 16-19, 1996  
ISSN: 0945-053X  
DT Conference; Abstract  
LA English

L32 ANSWER 12 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS  
DUPLICATE 6  
AN 1995-15419 BIOSIS  
DN PREV199598029719  
TI Type I collagen transgene used as a marker to trace donor \*\*\*marrow\*\*\* \*\*\*stroma\*\*\* 1 cells. Transplanted cells persist up to five months in bone marrow, spleen, cartilage and lung.  
AU Pereira, Ruth F. (1); Halford, Kenneth W.; O'Hara, Michael; Leeper, Dennis; Pollard, Marea; Sokolov, Boris; \*\*\*Prockop, Darwin J.\*\*\*  
CS (1) Dep. Biochem. Mol. Biol., Jefferson Med. Coll., Thomas Jefferson Univ., Philadelphia, PA 19107 USA  
SO Matrix Biology, (1994) Vol. 14, No. 5, pp. 407.  
Meeting Info.: Fifth International Conference on the Molecular Biology and Pathology of Matrix Philadelphia, Pennsylvania, USA June 19-22, 1994  
DT Conference  
LA English

=> d his

(FILE 'HOME' ENTERED AT 15:12:44 ON 18 OCT 1999)

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L1 142 S STROMA#(P)XEXOGENOUS GENE OR GENE  
CONSTRUCT OR VECTOR/AB,BI  
L2 26 S L1 AND PROMOTER#/AB,BI  
L3 1 S L2 AND COLLAGEN/AB,BI  
L4 14675 S MESENCHYM#/AB,BI  
L5 64 S L4(P)XGENE CONSTRUCT OR EXOGENOUS  
GENE OR VECTOR#/AB,BI  
L6 12 S L5 AND PROMOTER#/AB,BI  
L7 443 S STROMAL FIBROBLAST#/AB,BI  
L8 11 S L7(P)XVECTOR# OR CONSTRUCT#/AB,BI  
L9 398 S OBESITY GENE OR OBESITY PROTEIN OR OB  
GENE/AB,BI  
L10 1 S L9(10A)XCONSTRUCT OR VECTOR/AB,BI  
L11 0 S OB GENE AND (MESENCHYMAL OR MARROW  
STROMA# OR STROMAL FIBROBL  
L12 69 S LTM/C#  
L13 0 S L12 AND OB GENE/AB,BI  
L14 0 S L12 AND OBESITY FACTOR/AB,BI  
L15 9 S OBESITY FACTOR/AB,BI  
L16 1867 S LEPTIN/AB,BI  
L17 385 S L16 AND ADIPOCYTE#/AB,BI  
L18 8138 S ADIPOCYTE#/AB,BI  
L19 54 S L18(10A)XCONSTRUCT OR EXOGENOUS OR  
VECTOR/AB,BI  
L20 1 S L19 AND (OB GENE OR LEPTIN)/AB,BI  
L21 14812 S L1 OR L4  
L22 0 S L21 AND (OB GENE OR LEPTIN)/AB,BI

FILE MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS'  
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OCT 1999  
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L24 2 DUP REM L23 (0 DUPLICATES REMOVED)  
L25 9655 S OBESITY PROTEIN OR OBESITY FACTOR OR  
OBESITY GENE OR OB GENE  
L26 1681 S L25 AND (STROMA# OR MESENCHYMAL OR  
ADIPOCYTE#)/AB,BI  
L27 363 S L25 AND (CONSTRUCT# OR VECTOR# OR  
EXOGENOUS)/AB,BI  
L28 79 S L27 AND (STROMA# OR MESENCHYMAL OR  
ADIPOCYTE#)/AB,BI  
L29 35 DUP REM L28 (44 DUPLICATES REMOVED)  
E PROCKOP DARWIN J/AU  
L30 553 S E3-E4  
L31 18 S L30 AND (MARROW STROMA# OR  
MESENCHYMAL)/AB,BI  
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'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L33 0 L32 AND PROMOTER#/AB,BI

=> e pereira ruth f/au  
E1 1 PEREIRA RUSCHEL P/AU  
E2 14 PEREIRA RUTH/AU  
E3 11 -> PEREIRA RUTH F/AU  
E4 1 PEREIRA RUTH FRANCES/AU  
E5 1 PEREIRA RUJI FERNANDES/AU  
E6 2 PEREIRA RUY J/AU  
E7 212 PEREIRA S/AU  
E8 18 PEREIRA S A/AU  
E9 16 PEREIRA S C/AU  
E10 1 PEREIRA S C C/AU  
E11 7 PEREIRA S C S/AU  
E12 14 PEREIRA S D/AU

=> s e2-e4  
L34 26 (\*PEREIRA RUTH\*/AU OR \*PEREIRA RUTH F\*/AU  
OR \*PEREIRA RUTH FRANC  
ES\*/AU)  
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PROCESSING COMPLETED FOR L34  
L35 20 DUP REM L34 (6 DUPLICATES REMOVED)

=> s l35 and (marrow stroma# or mesenchymal)/ab,bi  
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'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L36 3 L35 AND (MARROW STROMA# OR  
MESENCHYMAL)/AB,BI

=> dup rem l36  
PROCESSING COMPLETED FOR L36  
L37 3 DUP REM L36 (0 DUPLICATES REMOVED)

=> d l- bib ab  
YOU HAVE REQUESTED DATA FROM 3 ANSWERS -  
CONTINUE? Y/(N)y

L37 ANSWER 1 OF 3 BIOSIS COPYRIGHT 1999 BIOSIS  
AN 1998:132318 BIOSIS  
DN PREV199800132318  
TI \*\*\*Marrow\*\*\* \*\*\*stromal\*\*\* cells as a source of  
progenitor cells  
for nonhematopoietic tissues in transgenic mice with a phenotype  
of  
osteogenesis imperfecta.  
AU \*\*\*Pereira, Ruth F.\*\*\*; O'Hara, Michael D.; Laptev, Alexey  
V.; Halford, Kenneth W.; Pollard, Marea D.; Class, Reiner; Simon,  
Daniela;  
Livezey, Kristin; Prockop, Darwin J. (1)  
CS (1) Cent. Gene Therapy, Allegheny Univ. Health Sci., 245 N. 15  
St., 10118  
NCB, Mail Stop 421, Philadelphia, PA 19102-1192 USA  
SO Proceedings of the National Academy of Sciences of the United  
States of

America, (Feb. 3, 1998) Vol. 95, No. 3, pp. 1142-1147.  
ISSN: 0027-8424.

DT Article

LA English

AB \*\*\*Marrow\*\*\* \*\*\*stromal\*\*\* cells from wild-type mice were infused into transgenic mice that had a phenotype of fragile bones resembling osteogenesis imperfecta because they expressed a human minigene for type I collagen. In mice that were irradiated with potentially lethal levels (700

cGy) or sublethal levels (350 cGy), DNA from the donor \*\*\*marrow\*\*\* \*\*\*stromal\*\*\* cells was detected consistently in marrow, bone, cartilage, and lung either 1 or 2.5 mo after the infusions. The DNA also

was detected but less frequently in the spleen, brain, and skin. There was a small but statistically significant increase in both collagen content and mineral content of bone 1 mo after the infusion.

Similar results were obtained with infusion of relatively large amounts of wild-type whole marrow cells into the transgenic mice. In

experiments in which male \*\*\*marrow\*\*\* \*\*\*stromal\*\*\* cells were infused into a

female osteogenesis imperfecta-transgenic mouse, fluorescence in situ

hybridization assays for the Y chromosome indicated that, after 2.5

mo, donor male cells accounted for 4-19% of the fibroblasts or fibroblast-like

cells obtained in primary cultures of the lung, calvaria, cartilage, long

bone, tail, and skin. In a parallel experiment in which whole marrow cells

from a male mouse were infused into a female immunodeficient rag-2 mouse,

donor male cells accounted for 4-6% of the fibroblasts or fibroblast-like

cells in primary cultures. The results support previous suggestions that

\*\*\*marrow\*\*\* \*\*\*stromal\*\*\* cells or related cells in marrow serve

as a source for continual renewal of cells or related cells in marrow serve as a source for continual renewal of cells in a number of

nonhematopoietic tissues.

L37 ANSWER 2 OF 3 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1997:46949 BIOSIS

DN PREV199799346152

TI Use of \*\*\*marrow\*\*\* \*\*\*stromal\*\*\* cells to replace bone cells in a

transgenic mouse model for osteogenesis imperfecta.

AU \*\*\*Pereira, Ruth F. (1)\*\*\*; Halford, Kenneth W. (1); O'Hara, Michael

D.; Pollard, Marea D.; Volpe, Patricia; Leptve, Alexey (1); Prockop,

Darwin J. (1)

CS (1) Thomas Jefferson Univ., Dep. Biochem., Philadelphia, PA USA

SO Matrix Biology, (1996) Vol. 15, No. 3, pp. 188.

Meeting Info.: Sixth International Conference on the Molecular Biology and

Pathology of Matrix Philadelphia, Pennsylvania, USA June 16-19, 1996

ISSN: 0945-053X

DT Conference; Abstract

LA English

L37 ANSWER 3 OF 3 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1995:15419 BIOSIS

DN PREV199598029719

TI Type I collagen transgene used as a marker to trace donor \*\*\*marrow\*\*\*

\*\*\*stroma\*\*\* 1 cells. Transplanted cells persist up to five months in

bone marrow, spleen, cartilage and lung.

AU \*\*\*Pereira, Ruth F. (1)\*\*\*; Halford, Kenneth W.; O'Hara, Michael;

Leeper, Dennis; Pollard, Marea; Sokolov, Boris; Prockop, Darwin J.

CS (1) Dep. Biochem. Mol. Biol., Jefferson Med. Coll., Thoams Jefferson Univ., Philadelphia, PA 19107 USA

SO Matrix Biology, (1994) Vol. 14, No. 5, pp. 407.

Meeting Info.: Fifth International Conference on the Molecular Biology and

Pathology of Matrix Philadelphia, Pennsylvania, USA June 19-22, 1994

DT Conference

LA English

=> e leeper dennis b/au

E1 2 LEEPER DAVID R/AU

E2 6 LEEPER DENNIS/AU

E3 34 --> LEEPER DENNIS B/AU

E4 1 LEEPER DOUGLAS A/AU

E5 1 LEEPER DONNA/AU

E6 4 LEEPER DOUGLAS A/AU

E7 29 LEEPER E/AU

E8 1 LEEPER ED/AU

E9 2 LEEPER F/AU

E10 76 LEEPER F J/AU

E11 1 LEEPER FINAN J/AU

E12 1 LEEPER FINIAN/AU

=> s e2-e3

L38 40 (\*LEEPPER DENNIS\*/AU OR \*LEEPPER DENNIS

B\*/AU)

=> s i38 and (marrow stroma# or mesenchymal)/ab,bi

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L39 21.38 AND (MARROW STROMA# OR

MESENCHYMAL)/AB,BI

=> dup rem i39

PROCESSING COMPLETED FOR L39

L40 1 DUP REM L39 (1 DUPLICATE REMOVED)

=> d bib ab

L40 ANSWER 1 OF 1 BIOSIS COPYRIGHT 1999 BIOSIS

DUPLICATE 1

AN 1995:15419 BIOSIS

DN PREV199598029719

TI Type I collagen transgene used as a marker to trace donor

\*\*\*marrow\*\*\*

\*\*\*stroma\*\*\* 1 cells. Transplanted cells persist up to five

months in

bone marrow, spleen, cartilage and lung.

AU Pereira, Ruth F. (1); Halford, Kenneth W.; O'Hara, Michael;

\*\*\*Leeper,\*\*\*

\*\*\* Dennis\*\*\*; Pollard, Marea; Sokolov, Boris; Prockop,

Darwin J.

CS (1) Dep. Biochem. Mol. Biol., Jefferson Med. Coll., Thoams Jefferson Univ., Philadelphia, PA 19107 USA

SO Matrix Biology, (1994) Vol. 14, No. 5, pp. 407.

Meeting Info.: Fifth International Conference on the Molecular Biology and

Pathology of Matrix Philadelphia, Pennsylvania, USA June 19-22,

1994

DT Conference

LA English

=> e o'hara michael d/au

MISMATCHED QUOTE IN EXPAND TERM

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MISMATCHED QUOTE IN EXPAND TERM

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Quotation marks (or apostrophes) must be used in pairs,

one before and one after the expression you are setting

off or masking.

=> e o'hara michael d/au

E1 7 OHARA MEGURU/AU

E2 1 OHARA MICA/AU

E3 0 --> OHARA MICHAEL D/AU

E4 1 OHARA MICHIKI/AU

E5 1 OHARA MICHIKO/AU

E6 61 OHARA MICHIMASA/AU

E7 6 OHARA MICHINORU/AU

E8 1 OHARA MICHIO/AU

E9 1 OHARA MICHIO/AU  
E10 7 OHARA MIE/AU  
E11 1 OHARA MIKHIKO CENTRAL KOTESAS/AU  
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E1 45 KULKOSKY J/AU  
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E3 27 --> KULKOSKY JOSEPH/AU  
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E5 1 KULKOSKY JOSEPH WILLIAM/AU  
E6 10 KULKOSKY P/AU  
E7 155 KULKOSKY P J/AU  
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L41 79 ("KULKOSKY J/AU OR "KULKOSKY J W/AU OR "KULKOSKY JOSEPH/AU OR "KULKOSKY JOSEPH W/AU OR "KULKOSKY JOSEPH WILLIAM/AU)  
=> s l41 and (marrow stroma# or mesenchymal)/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
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L42 0 L41 AND (MARROW STROMA# OR MESENCHYMAL)/AB,BI  
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E1 1 PHINNEY D P/AU  
E2 4 PHINNEY DAVID A/AU  
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E4 22 PHINNEY DONALD G/AU  
E5 1 PHINNEY DONALD GEORGE/AU  
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L43 26 ("PHINNEY DONALD/AU OR "PHINNEY DONALD G/AU OR "PHINNEY DONALD GEORGE"/AU)  
=> s l43 and (stroma# or mesenchymal)/ab,bi  
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PROCESSING COMPLETED FOR L44  
L45 6 DUP REM L44 (1 DUPLICATE REMOVED)  
=> d l - bib ab  
YOU HAVE REQUESTED DATA FROM 6 ANSWERS -  
CONTINUE? Y(N);Y  
L45 ANSWER 1 OF 6 INPADOC COPYRIGHT 1999  
EPDUPLICATE 1  
LEVEL 1  
AN 113045575 INPADOC ED 19990921 EW 199937 UP  
19990921 UW 199937  
TI ISOLATED \*\*\*STROMAL\*\*\* CELLS FOR USE IN THE  
TREATMENT OF DISEASES OF  
THE CENTRAL NERVOUS SYSTEM  
IN PROCKOP DARWIN J.; STOKES DAVID, G.; AZIZI, S.,  
AUSIM; PHINNEY,  
DONALD, G  
INS PROCKOP DARWIN J.; STOKES DAVID G; AZIZI S  
AUSIM; \*\*\*PHINNEY DONALD G\*\*\*  
INA US; US; US; US  
IPA MCP HAHNEMANN UNIVERSITY; PROCKOP, DARWIN,  
J.; STOKES, DAVID, G.; AZIZI,  
S, AUSIM; PHINNEY, DONALD, G  
PAS MCP HAHNEMANN UNIVERSITY; PROCKOP DARWIN  
J.; STOKES DAVID G; AZIZI S  
AUSIM; PHINNEY DONALD G  
PAA US; US; US; US; US  
TL English; French  
LA English  
DT Patent  
PIT WOA2 PUBL OF THE INT APPL WITHOUT INT SEARCH  
REP  
PI WO 9943286 A2 19990902  
DS RW: GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ  
MD RU TJ TM AT BE CH CY DE  
DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG  
CI CM GA GN GW ML  
MR NE SN TD TG  
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ  
DE DK EE ES FI GB GD GE  
GH GM HR HU ID IL IN IS JP KE KG KP KZ LC LK LR  
LS LT LU LV MD MG  
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL  
TJ TM TR TT UA UG US  
UZ VN YU ZW  
AI WO 1999-US3897 A 19990224  
PRAI US 1998-28395 A 19980224  
AB Methods of treating a human patient having a disease, disorder  
or  
condition of the central nervous system are disclosed. The methods  
include obtaining a bone marrow sample from a human donor,  
isolating

stromal cells from the bone marrow sample, and administering the  
isolated  
stromal cells to the central nervous system of the human patient,  
wherein  
the presence of the isolated stromal cells in the brain effects  
treatment  
of the disease, disorder or condition. Stromal cells which are  
isolated  
may be cultured in vitro, they may be genetically engineered to  
produce  
therapeutic compounds, and/or they may be pre-differentiated prior  
to  
administration into the central nervous system.  
L45 ANSWER 2 OF 6 CAPLUS COPYRIGHT 1999 ACS  
AN 1999-616004 CAPLUS  
TI Marrow \*\*\*stromal\*\*\* cells migrate throughout forebrain and  
cerebellum, and they differentiate into astrocytes after injection into  
neonatal mouse brains  
AU Kopen, Gene C.; Prockop, Darwin J.; \*\*\*Phinney, Donald  
G\*\*\*  
CS Center for Gene Therapy, MCP Hahnemann University,  
Philadelphia, PA,  
19102-1192, USA  
SO Proc. Natl. Acad. Sci. U. S. A. (1999), 96(19), 10711-10716  
CODEN: PNASA6; ISSN: 0027-8424  
PB National Academy of Sciences  
DT Journal  
LA English  
AB Stem cells are a valuable resource for treating disease, but limited  
access to stem cells from tissues such as brain restricts their utility.  
Here, we injected marrow \*\*\*stromal\*\*\* cells (MSCs) into the  
lateral  
ventricle of neonatal mice and asked whether these multipotential  
\*\*\*mesenchymal\*\*\* progenitors from bone marrow can adopt  
neural cell  
fates when exposed to the brain microenvironment. By 12 days  
postinjection, MSCs migrated throughout the forebrain and  
cerebellum  
without disruption to the host brain architecture. Some MSCs  
within the  
striatum and the mol. layer of the hippocampus expressed glial  
fibrillary  
acidic protein and, therefore, differentiated into mature astrocytes.  
MSCs also populated neuron rich regions including the islands of  
Calleja,  
the olfactory bulb, and the internal granular layer of the cerebellum.  
A large no. of MSCs also were found within the external granular  
layer of  
the cerebellum. In addn., neurofilament pos. donor cells were  
found  
within the reticular formation of the brain stem, suggesting that  
MSCs  
also may have differentiated into neurons. Therefore, MSCs are  
capable of  
producing differentiated progeny of a different dermal origin after



PIT EPAI PUBL. OF APPLICATION WITH SEARCH REPORT

bone, tail, and skin. In a parallel experiment in which whole

OSDW 96-497223

nonhematopoietic

OSDW 96-497223

L48 ANSWER 4 OF 4 INPADOC COPYRIGHT 1999 EPO  
LEVEL 1  
AN 46504721 INPADOC EW 199809 UW 199823  
TI ISOLATED \*\*\*STROMAL\*\*\* CELLS AND METHODS  
OF USING THE SAME  
IN PROCKOP, DARWIN J.; CARO, JOSE, KULKOSKY,  
JOSEPH; PEREIRA, RUTH F.;  
LEPPER, DENNIS B.; PHINNEY, DONALD; LAPTEV,  
ALEXEY; OHARA, MICHAEL D.  
INS PROCKOP DARWIN J.; CARO JOSE; KULKOSKY JOSEPH;  
PEREIRA RUTH F.; LEPPER  
DENNIS B.; PHINNEY DONALD; \*\*\*LAPTEV ALEXEY\*\*\*  
OHARA MICHAEL D  
INA US; US; US; US; US; US; US  
PA THOMAS JEFFERSON UNIVERSITY  
PAS UNIV JEFFERSON  
PAA US  
TL English; French  
LA English  
DT Patent  
PIT CAAA LAID-OPEN APPLICATION  
PI CA 2215143 AA 19961003  
AI CA 1996-2215143 A 19960328  
PRAI US 1995-412066 A 19950328  
US 1995-6627 P 19951113  
WO 1996-US4407 A 19960326

=> s (stroma#X(10aXpromoter#)ab,bi  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L49 163 (STROMA#X(10aXpromoter#)AB,BI

=> s l49(10aXcollagen)/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L50 4 L49(10aXCOLLAGEN)/AB,BI

=> dup rem l50  
PROCESSING COMPLETED FOR L50  
L51 1 DUP REM L50 (3 DUPLICATES REMOVED)

=> d bib ab

L51 ANSWER 1 OF 1 MEDLINE DUPLICATE 1  
AN 74172340 MEDLINE  
DN 74172340  
TI Control of corneal differentiation by extracellular materials  
\*\*\*Collagen\*\*\* as a \*\*\*promoter\*\*\* and stabilizer of  
epithelial  
\*\*\*stroma\*\*\* production.  
AU Meier S, Hay E D

SO DEVELOPMENTAL BIOLOGY, (1974 Jun) 38 (2) 249-70.  
Journal code: E7I ISSN: 0012-1606.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 197469

=> s l49(10aXprocollagen or col1a1 or col2a1)/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L52 0 L49(10aXPROCOLLAGEN OR COL1A1 OR  
COL2A1)/AB,BI

=> s (procollagen or col1a1 or col2a1X(wXpromoter#)ab,bi  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L53 200 (PROCOLLAGEN OR COL1A1 OR  
COL2A1X(WXPROMOTER#)AB,BI

=> s l53(pXobesity gene or ob gene or obesity protein or leptin)/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L54 0 L53(PYOBSITY GENE OR OB GENE OR OBESITY  
PROTEIN OR LEPTIN)/AB  
.BI

=> s l53(10aXstroma# or mesenchymal)/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L55 0 L53(10aXSTROMA# OR MESENCHYMAL)/AB,BI

=> s l53(10aXmarrow)/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L56 0 L53(10aXMARROW)/AB,BI

=> s l53(pXstroma# or mesenchymal)/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L57 4 L53(PYSTROMA# OR MESENCHYMAL)/AB,BI

=> dup rem l57  
PROCESSING COMPLETED FOR L57

L58 1 DUP REM L57 (3 DUPLICATES REMOVED)  
=> d bib ab

L58 ANSWER 1 OF 1 MEDLINE DUPLICATE 1  
AN 96066708 MEDLINE  
DN 96066708  
TI Stimulation of alpha 1 (I) procollagen gene expression in  
NIH-3T3 cells by  
the human T cell leukemia virus type 1 (HTLV-1) Tax gene  
AU Munoz E, Suri D, Amini S, Khalili K, Jimenez S A  
CS Department of Medicine, Jefferson Medical College, Thomas  
Jefferson  
University, Philadelphia, Pennsylvania 19107, USA..  
NC AM-19616 (NIADDK)  
AI-28272 (NIAD)  
SO JOURNAL OF CLINICAL INVESTIGATION, (1995 Nov) 96  
(5) 2413-20.  
Journal code: HS7 ISSN: 0021-9738.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals; Cancer  
Journals  
EM 199602

AB The mechanisms that regulate the expression of genes encoding  
extracellular matrix proteins in fibroblasts and other  
\*\*\*mesenchymal\*\*\*  
cells have remained elusive. Studies from several laboratories have  
indicated that Tax, a trans-regulatory protein from the human T cell  
leukemia virus type 1 not only augments viral gene expression but  
also  
triggers the expression of various cellular genes. Here, we  
examined the  
hypothesis that the expression of collagen genes may also be  
modulated by  
Tax. NIH-3T3 cells were simultaneously transfected with a Tax  
expressor  
plasmid and a chimeric construct containing regulatory sequences  
(-804 to  
+42 bp) of the alpha 1(I) procollagen gene ( \*\*\*COL1A1\*\*\* )  
\*\*\*promoter\*\*\*. The results indicated that the promoter activity  
of the  
-804 to bp COL1A1 fragment increased up to 12-fold in cells  
expressing  
Tax. Deletion analysis revealed that the region of COL1A1  
encompassing  
nucleotides -174 to -84 contained the Tax-responsive elements. A  
gene  
segment encompassing nucleotides -187 to -67, which contained  
this region,  
proved sufficient to confer Tax inducibility (2.5-fold) to a herpes  
simplex virus thymidine kinase promoter. Stably transfected  
NIH-3T3 cell  
clones that constitutively produce Tax displayed elevated levels of  
alpha  
1(I) procollagen and fibronectin transcripts and increased

production and accelerated processing of type I procollagen. These findings suggest that retroviral proteins may be involved in the pathogenesis of idiopathic diseases accompanied by collagen overproduction.

=> d his

(FILE 'HOME' ENTERED AT 15:12:44 ON 18 OCT 1999)

FILE 'MEDLINE' ENTERED AT 15:12:49 ON 18 OCT 1999  
L1 142 S STROMA#(P)EXOGENOUS GENE OR GENE  
CONSTRUCT OR VECTOR/AB,BI

L2 26 S L1 AND PROMOTER#/AB,BI

L3 1 S L2 AND COLLAGEN/AB,BI

L4 14675 S MESENCHYM#(P)AB,BI

L5 64 S L4(P)GENE CONSTRUCT OR EXOGENOUS  
GENE OR VECTOR/AB,BI

L6 12 S L5 AND PROMOTER#/AB,BI

L7 443 S STROMAL FIBROBLAST#/AB,BI

L8 11 S L7(P)VECTOR# OR CONSTRUCT#/AB,BI

L9 398 S OBESITY GENE OR OBESITY PROTEIN OR OB  
GENE/AB,BI

L10 1 S L4(10A)XCONSTRUCT OR VECTOR/AB,BI

L11 0 S OB GENE AND (MESENCHYMAL OR MARROW  
STROMA# OR STROMAL FIBROBL

L12 69 S L7MC#

L13 0 S L12 AND OB GENE/AB,BI

L14 0 S L12 AND OBESITY FACTOR/AB,BI

L15 9 S OBESITY FACTOR/AB,BI

L16 1867 S LEPTIN/AB,BI

L17 385 S L16 AND ADIPOCYTE#/AB,BI

L18 8138 S ADIPOCYTE#/AB,BI

L19 54 S L18(10A)XCONSTRUCT OR EXOGENOUS OR  
VECTOR/AB,BI

L20 1 S L19 AND (OB GENE OR LEPTIN)/AB,BI

L21 14812 S L1 OR L4

L22 0 S L21 AND (OB GENE OR LEPTIN)/AB,BI

FILE 'MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS'  
ENTERED AT 15:28:51 ON 18  
OCT 1999

L23 2 S L22

L24 2 DUP REM L23 (0 DUPLICATES REMOVED)

L25 9655 S OBESITY PROTEIN OR OBESITY FACTOR OR  
OBESITY GENE OR OB GENE

L26 1681 S L25 AND (STROMA# OR MESENCHYMAL OR  
ADIPOCYTE#/AB,BI

L27 363 S L25 AND (CONSTRUCT# OR VECTOR# OR  
EXOGENOUS)/AB,BI

L28 79 S L27 AND (STROMA# OR MESENCHYMAL OR  
ADIPOCYTE#/AB,BI

L29 35 DUP REM L28 (44 DUPLICATES REMOVED)

E PROCKOP DARWIN J/AU

L30 553 S E3-E4

L31 18 S L30 AND (MARROW STROMA# OR  
MESENCHYMAL)/AB,BI

L32 12 DUP REM L31 (6 DUPLICATES REMOVED)

L33 0 S L32 AND PROMOTER#/AB,BI

E PEREIRA RUTH F/AU

L34 26 S E2-E4

L35 20 DUP REM L34 (6 DUPLICATES REMOVED)

L36 3 S L35 AND (MARROW STROMA# OR  
MESENCHYMAL)/AB,BI

L37 3 DUP REM L36 (0 DUPLICATES REMOVED)

E LEEPER DENNIS B/AU

L38 40 S E2-E3

L39 2 S L38 AND (MARROW STROMA# OR  
MESENCHYMAL)/AB,BI

L40 1 DUP REM L39 (1 DUPLICATE REMOVED)

E OHARA MICHAEL D/AU

E KULKOSKY JOSEPH/AU

L41 79 S E1-E3

L42 0 S L41 AND (MARROW STROMA# OR  
MESENCHYMAL)/AB,BI

E PHINNEY DONALD/AU

L43 26 S E3-E5

L44 7 S L43 AND (STROMA# OR MESENCHYMAL)/AB,BI

L45 6 DUP REM L44 (1 DUPLICATE REMOVED)

E LAPTEV ALEXEY/AU

L46 15 S E1-E4

L47 0 S L46 AND (STROMA# OR MESENCHYMAL)/AB,BI

L48 4 DUP REM L47 (1 DUPLICATE REMOVED)

L49 163 S (STROMA#(10A)X(PROMOTER#/AB,BI

L50 4 S L49(10A)XCOLLAGEN/AB,BI

L51 1 DUP REM L50 (3 DUPLICATES REMOVED)

L52 0 S L49(10A)XPROCOLLAGEN OR COL1A1 OR  
COL2A1)/AB,BI

L53 200 S (PROCOLLAGEN OR COL1A1 OR  
COL2A1)X(WXPROMOTER#/AB,BI

L54 0 S L53(PYOBESITY GENE OR OB GENE OR  
OBESITY PROTEIN OR LEPTIN)

L55 0 S L53(10A)X(STROMA# OR MESENCHYMAL)/AB,BI

L56 0 S L53(10A)X(MARROW)/AB,BI

L57 4 S L53(P)X(STROMA# OR MESENCHYMAL)/AB,BI

L58 1 DUP REM L57 (3 DUPLICATES REMOVED)

=> s l53(p)(bone cell# or osteoblast# or preosteoblast#)/ab,bi

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

2 FILES SEARCHED...

'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE

L59 29 S L53(P)X(BONE CELL# OR OSTEOLAST# OR  
PREOSTEOBLAST#/AB,BI

=> dup rem l59

PROCESSING COMPLETED FOR L59

L60 8 DUP REM L59 (21 DUPLICATES REMOVED)

=> d l - bib ab

YOU HAVE REQUESTED DATA FROM 8 ANSWERS -

CONTINUE? Y/(N)y

L60 ANSWER 1 OF 8 MEDLINE

AN 1998241028 MEDLINE

DN 98241028

TI PTH-responsive osteoblast nuclear matrix architectural  
transcription

factor binds to the rat type I collagen promoter

AU Alvarez M, Thunyakitipal P, Morrison P, Onyia J, Hock J,  
Bidwell J P

CS Department of Oral Biology, Indiana University School of  
Dentistry,

Indianapolis 46202, USA.

NC R55DK48310 (NIDDK)

ROI DE07272 (NIDR)

SO JOURNAL OF CELLULAR BIOCHEMISTRY, (1998 Jun 1) 69

(3) 336-52.

Journal code: HNF. ISSN: 0730-2312.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199808

EW 19980802

AB In connective tissue, cell structure contributes to type I collagen  
expression. Differences in \*\*\*osteoblast\*\*\* microarchitecture  
may

account for the two distinct cis elements regulating basal  
expression, in

vivo and in vitro, of the rat type I collagen alpha1(I) polypeptide  
chain

(COL1A1). The \*\*\*COL1A1\*\*\* \*\*\*promoter\*\*\*  
conformation may be the

penultimate culmination of \*\*\*osteoblast\*\*\* structure.

Architectural

transcription factors bind to the minor groove of AT-rich DNA and  
bend it,

altering interactions between other trans-acting proteins. Similarly,  
nuclear matrix (NM) proteins bind to the minor groove of AT-rich

matrix-attachment regions, regulating transcription by altering DNA  
structure. We propose that \*\*\*osteoblast\*\*\* NM architectural

transcription factors link cell structure to promoter geometry and  
COL1A1

transcription. Our objective was to identify potential  
\*\*\*osteoblast\*\*\*

NM architectural transcription factors near the in vitro and in vivo  
regulatory regions of the rat \*\*\*COL1A1\*\*\* \*\*\*promoter\*\*\*

Nuclear

protein-promoter interactions were analyzed by gel shift analysis  
and

related techniques. NM extracts were derived from rat  
osteosarcoma cells

and from rat bone. The NM protein, NMP4, and a soluble nuclear  
protein,

NP, both bound to two homologous poly(dT) elements within the  
COL1A1 in

vitro regulatory region and proximal to the in vivo regulatory

element.  
These proteins bound within the minor groove and bent the DNA.  
Parathyroid hormone increased NP/NMP4 binding to both poly(dT) elements and decreased COL1A1 mRNA in the osteosarcoma cells. NP/NMP4-\*\*\*promoter\*\*\* interactions may represent a molecular pathway by which \*\*\*osteoblast\*\*\* structure is coupled to COL1A1 expression.

L60 ANSWER 2 OF 8 MEDLINE DUPLICATE 2  
AN 1998322114 MEDLINE  
DN 98322114  
TI 1,25-Dihydroxyvitamin D3 inhibition of col1a1 promoter expression in calvariae from neonatal transgenic mice.  
AU Bedalov A; Salvatori R; Dodig M; Kapural B; Pavlin D; Kream B E; Clark S  
CS Department of Pediatrics, MC1515, University of Connecticut Health Center,  
263 Farmington Ave., Farmington, CT 06030, USA.  
NC AR29983 (NIAMS)  
AR38933 (NIAMS)  
AR2985 (NIAMS)  
SO BIOCHIMICA ET BIOPHYSICA ACTA, (1998 Jul 9) 1398 (3) 285-93.  
Journal code: AOW. ISSN: 0006-3002.  
CY Netherlands  
DT Journal, Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals, Cancer Journals  
EM 199810  
EW 19981004  
AB We studied the effect of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) on organ cultures of transgenic mouse calvariae containing segments of the \*\*\*Col1a1\*\*\* \*\*\*promoter\*\*\* extending to -3518, -2297, -1997, -1794, -1763, and -1719 bp upstream of the transcription start site fused to the chloramphenicol acetyltransferase (CAT) reporter gene. 1,25(OH)2D3 had a dose-dependent inhibitory effect on the expression of the -3518 bp promoter construct (ColCAT3.6), with maximal inhibition of about 50% at 10 nM. This level of inhibition was consistent with the previously observed effect on the endogenous Col1a1 gene in \*\*\*bone\*\*\* \*\*\*cell\*\*\* models. All of the shorter constructs were also inhibited by 10 nM 1,25(OH)2D3, suggesting that the sequences required for 1,25(OH)2D3 inhibition are downstream of -1719 bp. The inhibitory effect of 1,25(OH)2D3 on transgene mRNA was maintained in the presence of the

protein synthesis inhibitor cycloheximide, suggesting that the inhibitory effect on Col1a1 gene transcription does not require de novo protein synthesis. We also examined the in vivo effect of 1,25(OH)2D3 treatment of transgenic mice on ColCAT activity, and found that 48 h treatment caused a dose-dependent inhibition of CAT activity in calvariae comparable to that observed in organ cultures. In conclusion, we demonstrated that 1,25(OH)2D3 inhibits \*\*\*Col1a1\*\*\* \*\*\*promoter\*\*\* transgenic mouse calvariae, both in vivo and in vitro. The results indicate that there is a 1,25(OH)2D3 responsive element downstream of -1719 bp. The inhibitory effect does not require new protein synthesis.

L60 ANSWER 3 OF 8 MEDLINE DUPLICATE 3  
AN 97131981 MEDLINE  
DN 97131981  
TI Rat osteoblast and osteosarcoma nuclear matrix proteins bind with specificity to the rat type I collagen promoter.  
AU Alvarez M; Long H; Onyia J; Hock J; Xu W; Bidwell J  
CS Department of Oral Biology, Indiana University School of Dentistry,  
Indianapolis 46202, USA.  
NC R55-DK-48310 (NIDDK)  
R01-DE-07272 (NIDR)  
SO ENDOCRINOLOGY, (1997 Jan) 138 (1) 482-9.  
Journal code: EGZ. ISSN: 0013-7227.  
CY United States  
DT Journal, Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals, Priority Journals, Cancer Journals  
EM 199703  
EW 19970304  
AB The nuclear matrix mediates the 3-dimensional organization of DNA and supports DNA replication and its transcription. We hypothesize that the \*\*\*osteoblast\*\*\* nuclear matrix contributes to the transcriptional control of type I collagen (COL1A1) expression. Cis-regulatory elements of the rat \*\*\*COL1A1\*\*\* \*\*\*promoter\*\*\* that control \*\*\*osteoblast\*\*\* expression in vivo are between -2.3 and -1.67 kilobase pairs (kb) but lie within -3.5 and -2.3 kb in cultured \*\*\*bone\*\*\* \*\*\*cells\*\*\*. This may result from differences in cell architecture between \*\*\*osteoblasts\*\*\* in tissue and those in vitro. Our aim was to identify \*\*\*osteoblast\*\*\* nuclear matrix proteins (NMPs) that

associated with sequence-specificity to the \*\*\*COL1A1\*\*\* \*\*\*promoter\*\*\*. We used \*\*\*osteoblasts\*\*\* from the rat femur and the rat osteosarcoma cells, ROS 17/2.8. Nuclear matrix and soluble nuclear proteins were obtained as separate subfractions. Gel mobility shift analysis, using fragments of the \*\*\*COL1A1\*\*\* \*\*\*promoter\*\*\*, was used to identify DNA-binding proteins in the nuclear subfractions. A NMP-DNA interaction, NMP3, was observed between -2149 and -2106 nucleotide in both \*\*\*osteoblasts\*\*\* and osteosarcoma cells. NMP4 was detected between -3518 to -3406 nucleotide. Therefore, \*\*\*osteoblast\*\*\* NMPs recognize sequences in regulatory regions of the \*\*\*COL1A1\*\*\* \*\*\*promoter\*\*\* and may link cell structure and the transcriptional regulation of this protein.

L60 ANSWER 4 OF 8 BIOSIS COPYRIGHT 1999 BIOSIS  
AN 1998:20020 BIOSIS  
DN PREV199800020020  
TI The \*\*\*osteoblast\*\*\* nuclear matrix (NM) protein, NMP4, binds the type I collagen ( \*\*\*COL1A1\*\*\* ) \*\*\*promoter\*\*\*.  
AU Thumyakitpal, P.; Alvarez, M.; Morrison, P.; Onyia, J.; Hock, J.; Bidwell, J. P.  
CS Indiana Univ. Sch. Dent., Indianapolis, IN 46202 USA  
SO Molecular Biology of the Cell, (Nov., 1997) Vol. 8, No. SUPPL., pp. 102A.  
Meeting Info.: 37th Annual Meeting of the American Society for Cell Biology  
Biology Washington, D.C., USA December 13-17, 1997 American Society for Cell Biology  
DT Conference  
LA English  
ISSN: 1059-1524.

L60 ANSWER 5 OF 8 MEDLINE DUPLICATE 4  
AN 96279197 MEDLINE  
DN 96279197  
TI Identification of a TAAAT-containing motif required for high level expression of the \*\*\*COL1A1\*\*\* \*\*\*promoter\*\*\* in differentiated \*\*\*osteoblasts\*\*\* of transgenic mice.  
AU Dodig M; Kronenberg M S; Bedalov A; Kream B E; Gronowicz G; Clark S H; Maek K; Liu Y H; Maxon R; Pan Z Z; Upholt W B; Rowe D W; Lichter A C  
CS Department of Pediatrics, University of Connecticut Health Center,  
Farmington, Connecticut 06030, the Department.  
NC AR29983 (NIAMS)  
AR38933 (NIAMS)



AR29850 (NIAMS)

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Jul 5) 271 (27) 16422-9

Journal code: HIV ISSN: 0021-9258

CY United States

DT Journal, Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199610

AB Our previous studies have shown that the 49-base pair region of promoter DNA between -1719 and -1670 base pairs is necessary for transcription of

the rat COL1A1 gene in transgenic mouse calvariae. In this study, we further define this element to the 13-base pair region between -1683 and -1670. This element contains a TAAAT motif that binds homeodomain-containing proteins. Site-directed mutagenesis of this element in the context of a COL1A1-chloramphenicol acetyltransferase construct extending to -3518 base pairs decreased the ratio of reporter gene activity in calvariae to tendon from 3:1 to 1:1, suggesting a preferential effect on

activity in calvariae. Moreover, chloramphenicol acetyltransferase-specific immunofluorescence microscopy of transgenic calvariae showed that the mutation preferentially reduced levels of chloramphenicol acetyltransferase protein in differentiated \*\*\*osteoblasts\*\*\*. Gel mobility shift assays demonstrate that differentiated \*\*\*osteoblasts\*\*\* contain a nuclear factor that binds to this site. This binding activity is not present in undifferentiated \*\*\*osteoblasts\*\*\*. We show that Mx2, a homeodomain protein, binds to this motif; however, Northern analysis revealed that Mx2 mRNA is present in undifferentiated \*\*\*bone\*\*\* cells but not in fully differentiated \*\*\*osteoblasts\*\*\*. In addition, cotransfection studies in ROS 17/2.8 osteosarcoma cells using an Mx2 expression vector showed that Mx2

inhibits a \*\*\*COL1A1\*\*\* promoter\*\*\*-chloramphenicol acetyltransferase construct. Our results suggest that high COL1A1 expression in bone is mediated by a protein that is induced during \*\*\*osteoblast\*\*\* differentiation. This protein may contain a homeodomain; however, it is distinct from homeodomain proteins reported previously to be present in bone.

L60 ANSWER 6 OF 8 MEDLINE

AN 95197712 MEDLINE

DUPLICATE 5

DN 95197712

TI Analysis of regulatory regions in the COL1A1 gene responsible for 1,25-dihydroxyvitamin D3-mediated transcriptional repression in osteoblastic cells.

AU Pavlin D, Bedalov A, Kronenberg M S, Kream B E, Rowe D W, Smith C L, Pike J W, Lichter A C

CS Department of Orthodontics, University of Texas Health Science Center, San Antonio 78284.

NC AR29983 (NIAMS)

AR38933 (NIAMS)

AR29850 (NIAMS)

SO JOURNAL OF CELLULAR BIOCHEMISTRY, (1994 Dec) 56 (4) 490-501.

Journal code: HNF ISSN: 0730-2312

CY United States

DT Journal, Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199506

AB The synthesis of type I collagen in \*\*\*bone\*\*\* cells\*\*\* is inhibited by the calcium-regulating hormone 1,25-dihydroxyvitamin D3.

Earlier work from our laboratories has indicated that vitamin D regulation is at the level of transcription, based on results from both nuclear run-off assays and functional promoter analysis of a hybrid gene consisting of a 3.6 kb \*\*\*COL1A1\*\*\* promoter\*\*\* fragment fused to the chloramphenicol acetyltransferase reporter gene. In the present study, we investigated the molecular basis for vitamin D-mediated transcriptional repression of the COL1A1 gene and report the identification of a region within the COL1A1 upstream promoter (the HindIII-PstI restriction fragment between nucleotides -2295 and -1670) which is necessary for 1,25-dihydroxyvitamin D3 responsiveness in osteoblastic cells. This hormone-mediated inhibitory effect on the marker gene parallels the inhibition of the endogenous collagen gene. A 41 bp fragment from this region (between nucleotides -2256 and -2216) contains a sequence which is very similar to vitamin D-responsive elements identified in the osteocalcin gene. Extracts from cultured cells which express a high level of vitamin D receptor contain a hormone receptor complex that binds specifically to this 41 bp fragment, as demonstrated by bandshift analysis. However, deletion of this vitamin D receptor binding region from

either a -3.5 kb or a -2.3 kb promoter fragment did not abolish vitamin D responsiveness. These results indicate that a vitamin D response element similar to that described for other vitamin D responsive genes (osteocalcin and osteopontin) does not alone mediate the repression of COL1A1 by 1,25-dihydroxyvitamin D3.

L60 ANSWER 7 OF 8 MEDLINE

AN 93360953 MEDLINE

DN 93360953

TI Transgenic expression of COL1A1-chloramphenicol acetyltransferase fusion genes in bone: differential utilization of promoter elements in vivo and in cultured cells.

AU Krebsbach P H, Harrison J R, Lichter A C, Woody C O, Rowe D W, Kream B E

CS Department of Periodontology, University of Connecticut Health Center, Farmington 06030

NC AR29983 (NIAMS)

AR29850 (NIAMS)

AR38933 (NIAMS)

SO MOLECULAR AND CELLULAR BIOLOGY, (1993 Sep) 13 (9) 5168-74.

Journal code: NGY ISSN: 0270-7306

CY United States

DT Journal, Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199311

AB To directly compare the patterns of collagen promoter expression in cells and tissues, the activity of COL1A1 fusion genes in calvariae of neonatal transgenic mice and in primary \*\*\*bone\*\*\* cells\*\*\* derived by sequential digestion of transgenic calvariae was measured.

ColCAT3.6 contains 3.6 kb (positions -3521 to +115) of the rat COL1A1 gene ligated to the chloramphenicol acetyltransferase (CAT) reporter gene.

ColCAT2.3 and ColCAT1.7 are 5' deletion mutants which contain 2,296 and 1,672 bp, respectively, of COL1A1 DNA upstream from the transcription start site. ColCAT3.6 activity was 4- to 6-fold lower in primary \*\*\*bone\*\*\* cultures than in intact calvariae, while ColCAT2.3 activity was at least 100-fold lower in primary \*\*\*bone\*\*\* cultures than in calvariae. These changes were accompanied by a

threefold decrease in collagen synthesis and COL1A1 mRNA levels in primary \*\*\*bone\*\*\* compared with collagen synthesis and COL1A1 mRNA levels in freshly isolated calvariae. ColCAT3.6 and ColCAT2.3 activity was maintained in calvariae cultured in the presence or absence of serum for 4 to 7 days. Thus, when \*\*\*bone\*\*\* \*\*cells\*\*\* are removed from their normal microenvironment, there is parallel downregulation of collagen synthesis, collagen mRNA levels, and activity, with a much greater decrease in ColCAT2.3. These data suggest that a 624-bp region of the \*\*\*COL1A1\*\*\* \*\*\*promoter\*\*\* between positions -2296 and -1672 is active in intact and cultured bone but inactive in cultured cells derived from the bone. We suggest that the downregulation of COL1A1 activity in primary \*\*\*bone\*\*\* \*\*cells\*\*\* may be due to the loss of cell shape or to alterations in cell-cell and/or cell-matrix interactions that normally occur in intact bone.

L60 ANSWER 8 OF 8 MEDLINE DUPLICATE 7  
AN 92112960 MEDLINE  
DN 92112960  
TI Differential utilization of regulatory domains within the alpha 1(I) collagen promoter in osseous and fibroblastic cells.  
AU Pavlin D; Lichter A C; Bedalov A; Kream B E; Harrison J R; Thomas H F; Gronowicz G A; Clark S H; Woody C O; Rowe D W  
CS Department of Pediatrics, University of Connecticut Health Center, Farmington 06032  
NC AR38933 (NIAMS) AR39850 (NIAMS)  
1 KM DE00239 (NIDR)  
SO JOURNAL OF CELL BIOLOGY, (1992 Jan) 116 (1) 227-36.  
Journal code: HMBV, ISSN: 0021-9525.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199204  
AB Type I collagen is expressed in a variety of connective tissue cells and its transcriptional regulation is highly complex because of the influence of numerous developmental, environmental, and hormonal factors. To investigate the molecular basis for one aspect of this complex regulation, the expression of alpha 1(I) collagen (COL1A1) gene in osseous tissues, we

fused a 3.6-kb DNA fragment between bases -3,521 and +115 of the rat \*\*\*COL1A1\*\*\* \*\*\*promoter\*\*\*, and three deletion mutants, to the chloramphenicol acetyltransferase (CAT) marker gene. The expression of these ColCAT transgenes was measured in stably transfected osteoblastic cell lines ROS 17/2.8, Py-la, and MC3T3-E1 and three fibroblastic lines NIH-3T3, Rat-1, and EL2. Deletion of the distal 1.2-kb fragment of the full-length ColCAT 3.6 construct reduced the promoter activity 7- to 30-fold in the osteoblastic cell lines, twofold in EL2 and had no effect in NIH-3T3 and Rat-1 cells. To begin to assess the function of COL1A1 upstream regulatory elements in intact animals, we established transgenic mouse lines and examined the activity of the ColCAT3.6 construct in various tissues of newborn animals. The expression of this construct followed the expected distribution between the high and low collagen-producing tissues: high levels of CAT activity in calvarial bone, tooth, and tendon, a low level in skin, and no detectable activity in liver and brain. Furthermore, CAT activity in calvarial bone was three- to fourfold higher than that in the adjacent periosteal layer. Immunostaining for CAT protein in calvaria and developing tooth germ of ColCAT3.6 mice also confirmed the preferred expression of the transgene in differentiated \*\*\*osteoblasts\*\*\* and odontoblasts compared to fibroblast-like cells of periosteum and dental papilla. This study suggests that the 3.6-kb DNA fragment confers the strong expression of COL1A1 gene in high collagen producing tissues of intact animals and that the 5' flanking promoter sequence between -3,521 and -2,295 bp contains one or more stimulatory elements which are preferentially active in osteoblastic cells.

=> s col2a1/ab,bi  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L61 893 COL2A1/AB,BI  
=> s col2a1 promoter/ab,bi  
'AB' IS NOT A VALID FIELD CODE

'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
'AB' IS NOT A VALID FIELD CODE  
L62 24 COL2A1 PROMOTER/AB,BI  
=> dup rem l62  
PROCESSING COMPLETED FOR L62  
L63 12 DUP REM L62 (12 DUPLICATES REMOVED)  
=> d l- bib ab  
YOU HAVE REQUESTED DATA FROM 12 ANSWERS -  
CONTINUE? Y(N)?

L63 ANSWER 1 OF 12 CAPLUS COPYRIGHT 1999 ACS  
AN 1999-445332 CAPLUS  
DN 131-69064  
TI A functional analysis of the \*\*\*COL2A1\*\*\* \*\*\*promoter\*\*\* : the transcription factor delta-EF1 is involved in E2 box-mediated repression of COL2A1 gene transcription  
AU Murray, Darryl Maurice  
CS Johns Hopkins Univ., Baltimore, MD, USA  
SO (1999) 85 pp. Avail.: UMI, Order No. DA9920766  
From: Diss. Abstr. Int., B 1999, 60(2), 499  
DT Dissertation  
LA English  
AB Unavailable  
L63 ANSWER 2 OF 12 MEDLINE DUPLICATE 1  
AN 1999296490 MEDLINE  
DN 99296490  
TI SV40 large T antigen expression driven by col2a1 regulatory sequences immortalizes articular chondrocytes but does not allow stabilization of type II collagen expression.  
AU Steimberg N; Viengchareun S; Biehlmann F; Guenat I; Mignotte B; Adolphe M; Thonet S  
CS Ecole Pratique des Hautes Etudes, Laboratoire de Pharmacologie Cellulaire, Centre de Recherches Biomedicales des Cordeliers, 15 rue de l'Ecole de Medecine, Paris, 75006, France.  
SO EXPERIMENTAL CELL RESEARCH, (1999 Jun 15) 249 (2) 248-59.  
Journal code: EPB, ISSN: 0014-4827.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199909  
EW 19990902  
AB Immortalization of chondrocytes by SV40 T Ag has often been reported to

trigger the loss of expression of type II collagen, one of the main differentiation markers, although some immortalized chondrocyte lines maintaining a differentiated phenotype have also been described. Here, we show using transient cotransfections in differentiated chondrocytes that,

in contrast to c-src, neither SV40 T Ag, nor c-myc, decreases col2a1

transcriptional activity. Then, we report the possibility of immortalizing

rabbit articular chondrocytes by expression of SV40 T Ag controlled by the

\*\*\*col2a1\*\*\* \*\*\*promoter\*\*\* and enhancer (pCol2SV).

This strategy

allows one to select within a population of differentiated chondrocytes

those which are able to maintain functional regulation of the col2a1 gene

through long-term culture. In precisis pCol2SV-transfected chondrocytes,

all-trans-retinoic acid, a down-regulator of col2a1 expression, induced

apoptosis, strongly suggesting the strict control of T Ag expression by

col2a1 regulatory sequences. Some pCol2SV-transfected chondrocytes were

definitively immortalized, after a short crisis period. However, type

II collagen synthesis was restricted to a small proportion of cells, which

went on to decrease with subculture, while the proportion of cells expressing T Ag was not affected. In these postcrisis cells, T Ag

remained at least partially under the control of functional col2a1 regulatory elements as assessed by all-trans-retinoic acid down-regulation.

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L63 ANSWER 3 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1998-468445 BIOSIS

DN PREV199800468445

TI Stimulation of Sp1 DNA binding activity recognizing the human

type II

procollagen gene ( \*\*\*COL2A1\*\*\* ) \*\*\*promoter\*\*\* by

tumor necrosis

factor alpha(TNF-alpha) in cultured human chondrocytes

AU Liu, Gang; Dharmavaram, Rita; Jimenez, Sergio

CS Div. Rheumatol. Jefferson Med. Coll., Thomas Jefferson Univ.,

Philadelphia, PA 19107 USA

SO Arthritis & Rheumatism, (Sept., 1998) Vol. 41, No. 9 SUPPL.,

pp. S43.

Meeting Info.: 62nd National Scientific Meeting of the American College of

Rheumatology and the 33rd National Scientific Meeting of the Association

of Rheumatology Health Professionals San Diego, California, USA November

8-12, 1998 American College of Rheumatology

. ISSN: 0004-3591.

DT Conference

LA English

L63 ANSWER 4 OF 12 MEDLINE DUPLICATE

2

AN 1998001661 MEDLINE

DN 98001661

TI Detection and characterization of Sp1 binding activity in human

chondrocytes and its alterations during chondrocyte

dedifferentiation.

AU Dharmavaram R M; Liu G; Mowers S D; Jimenez S A

CS Division of Rheumatology, Department of Medicine, Jefferson Medical

College, Thomas Jefferson University, Philadelphia, Pennsylvania

19107,

USA.

NC AR39740 (NIAMS)

AR07583 (NIAMS)

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Oct 24)

272 (43) 26918-25.

Journal code: HIV. ISSN: 0021-9258.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199802

EW 19980204

AB We have detected DNA binding activity for a synthetic

oligonucleotide

containing an Sp1 consensus sequence in nuclear extracts from

human chondrocytes. Changes in the levels of Sp1 oligonucleotide-binding

activity were examined in nuclear extracts from freshly isolated

human chondrocytes, from chondrocytes that had been cultured under

conditions that allowed the maintenance of a chondrocyte-specific phenotype

on plastic dishes coated with the hydrogel poly(2-hydroxyethyl

methacrylate), and from chondrocytes induced to dedifferentiate into

fibroblast-like cells by passage in monolayer culture on plastic substrata. It was

observed that Sp1 binding was 2-3-fold greater in nuclear extracts

from dedifferentiated chondrocytes than in nuclear extracts from either

freshly isolated chondrocytes or from cells cultured in suspension. The Sp1

binding activity was specific, since it was competed by unlabeled

Sp1 but not by AP1 or AP2. The addition of a polyclonal antibody against

Sp1 to nuclear extracts from freshly isolated chondrocytes or to extracts

isolated from chondrocytes cultured in monolayer decreased the binding of

Sp1 by approximately 85%. However, when the same experiment was carried

out with nuclear extracts prepared from cells cultured on poly(2-hydroxyethyl methacrylate)-coated plates, only a very slight

inhibition of Sp1 binding was observed. When fragments of the \*\*\*COL2A1\*\*\* \*\*\*promoter\*\*\* containing putative Sp1

binding sites

amplified by polymerase chain reaction were examined, it was found that

the amounts of DNA-protein complex formed with nuclear extracts from

dedifferentiated chondrocytes were 2-3-fold greater than the amounts

formed with nuclear extracts from freshly isolated chondrocytes or from

cells cultured in suspension. Quantitation of DNA binding activity by

titration experiments demonstrated that nuclear extracts from fibroblast-like cells contained approximately 2-fold greater Sp1

specific

binding activity than nuclear extracts from chondrocytes. The direct

role of Sp1 in type II collagen gene transcription was demonstrated by

co-transfection experiments of \*\*\*COL2A1\*\*\*

\*\*\*promoter\*\*\* -CAT

constructs in Drosophila Schneider line L2 cells that lack Sp1

homologs. This is the first demonstration of Sp1 binding activity in human

chondrocytes and of differences in Sp1 DNA binding activity between

differentiated and dedifferentiated chondrocytes.

L63 ANSWER 5 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1998-157507 BIOSIS

DN PREV199800157507

TI Regulation of type II procollagen gene ( \*\*\*COL2A1\*\*\* )

\*\*\*promoter\*\*\*

by transcription factor SP1 and quantitation of alterations in SP1

binding activity in normal human chondrocytes and during chondrocyte

dedifferentiation.

AU Dharmavaram, Rita M.; Liu, Gang; Jimenez, Sergio A.

CS Dep. Med. Rheumatol. Div., Thomas Jefferson Univ.,

Philadelphia, PA 19107

USA

SO Arthritis & Rheumatism, (Sept., 1997) Vol. 40, No. 9 SUPPL.,

pp. S127.

Meeting Info.: 61st National Scientific Meeting of the American College of

Rheumatology and the 32nd National Scientific Meeting of the Association

of Rheumatology Health Professionals Washington, DC, USA November 8-12,

1997 Association of Rheumatology Health Professionals . ISSN: 0004-3591.

- DT Conference  
LA English
- L63 ANSWER 6 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS  
AN 1997:97903 BIOSIS  
DN PREV19979397106  
TI Minimal cis-acting elements for chondrocyte-specific expression of the mouse pro-alpha-1(I) collagen gene in transgenic mice.  
AU Zhou, Guang, Lefebvre, Veronique; Mukhopadhyay, Krish; Smith, Chad; Zhang, Zhaoping; Eberspaecher, Heidi; Garofalo, Silvio; De Crombrughe, Benoit  
CS Dep. Mol. Genet., Univ. Texas, M.D. Anderson Cancer Cent., Houston, TX  
77030 USA  
SO Molecular Biology of the Cell, (1996) Vol. 7, No. SUPPL., pp. 620A.  
Meeting Info.: Annual Meeting of the 6th International Congress on Cell Biology and the 36th American Society for Cell Biology San Francisco, California, USA December 7-11, 1996  
ISSN: 1059-1524  
DT Conference; Abstract; Conference  
LA English
- L63 ANSWER 7 OF 12 CAPLUS COPYRIGHT 1999 ACS  
AN 1996:482269 CAPLUS  
DN 125:134714  
TI A 47-bp sequence of the first intron of the mouse pro alpha 1(I) collagen gene is sufficient to direct chondrocyte expression  
AU Lefebvre, Veronique; Mukhopadhyay, Krish; Zhou, Guang; Garofalo, Silvio; Smith, Chad; Eberspaecher, Heidi; Kimura, James H.; de Crombrughe, Benoit  
CS M.D. Anderson Cancer Center, University Texas, Houston, TX, 77030, USA  
SO Ann. N. Y. Acad. Sci. (1996), 785(Molecular and Developmental Biology of Cartilage), 284-287  
CODEN: ANYAA9; ISSN: 0077-8923  
DT Journal  
LA English  
AB Promoter deletion anal. showed that a 47-bp sequence of the Col2a1 gene 1st intron contains cis-acting sequences that are sufficient for activation in chondrocytes and that the \*\*\*Col2a1\*\*\* does not contain sequences necessary for chondrocyte expression.  
L63 ANSWER 8 OF 12 MEDLINE  
3 AN 96070901 MEDLINE  
DN 96070901
- TI Use of a new rat chondrosarcoma cell line to delineate a 119-base pair chondrocyte-specific enhancer element and to define active promoter segments in the mouse pro-alpha 1(II) collagen gene.  
AU Mukhopadhyay K; Lefebvre V; Zhou G; Garofalo S; Kimura J H; de Crombrughe B  
CS Department of Molecular Genetics, University of Texas, M. D. Anderson Cancer Center, Houston 77030, USA.  
NC AR 40335 (NIAMS)  
AR 42909 (NIAMS)  
CA16672 (NCI)  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Nov 17) 270 (46) 27711-9  
Journal code: HIV. ISSN: 0021-9258.  
CY United States  
DT Journal, Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199603  
AB We show that a new rat chondrosarcoma (RCS) cell line established in long-term culture from the Swarm tumor displayed a stable differentiated chondrocyte-like phenotype. Indeed, these cells produced the collagen types II, IX, and XI and alcian blue-stainable cartilage-specific proteoglycans, but no type I or type III collagen. To functionally characterize their chondrocytic nature, the cells were stably transfected with a type II collagen/beta geo chimeric gene which confers essentially perfect chondrocyte-specific expression in transgenic mice. RCS cells expressed both beta-galactosidase and G418 resistance, in comparison with similarly transfected 10T1/2 and NIH/3T3 fibroblasts which did not. These cells were then used to perform a systematic deletion analysis of the first intron of the mouse type II collagen gene (Col2a1) using transient expression experiments to determine which segments stimulated expression of a luciferase reporter gene in RCS cells but not in 10T1/2 fibroblasts.  
Cloning of two tandem copies of a 156-base pair (bp) intron 1 fragment (+2188 to +2343) in a construction containing a 314-bp \*\*\*Col2a1\*\*\* caused an almost 200-fold increase in promoter activity in RCS cells but no increase in 10T1/2 cells. DNase I footprint analysis over this 156-bp fragment revealed two adjacent protected regions,  
FP1 and FP2, located in the 3'-half of this segment, but no differences were seen with nuclear extracts of RCS cells and 10T1/2 fibroblasts. Deletion of FP2 to leave a 119-bp segment decreased enhancer activity by several-fold, but RCS cell specificity was maintained. Further deletions indicated that sequences both in the 5' part of the 119-bp fragment and in FP1 were needed simultaneously for RCS cell-specific enhancer activity. A series of deletions in the promoter region of the mouse Col2a1 gene progressively reduced activity when these promoters were tested by themselves in transient expression experiments. However, these promoter deletions were all activated to a similar level in RCS cells by a 231-bp intron 1 fragment that included the 156-bp enhancer. The RCS cell-specific activity persisted even if the \*\*\*Col2a1\*\*\* \*\*\*promoter\*\*\* was replaced by a minimal adenovirus major late promoter. This 231-bp intron 1 fragment also had strong enhancing activity in transiently transfected mouse primary chondrocytes. Our experiments establish the usefulness of RCS cells as an experimental system for studies of the control of chondrocyte-specific genes, provide an extensive delineation of segments in the Col2a1 first intron involved in chondrocyte-specific activity, and show that promoter sequences are dispensable for chondrocyte specificity.  
L63 ANSWER 9 OF 12 MEDLINE  
4 AN 96360245 MEDLINE  
DN 96360245  
TI A 182 bp fragment of the mouse pro alpha 1(II) collagen gene is sufficient to direct chondrocyte expression in transgenic mice.  
AU Zhou G; Garofalo S; Mukhopadhyay K; Lefebvre V; Smith C N; Eberspaecher H; de Crombrughe B  
CS Department of Molecular Genetics, University of Texas, M. D. Anderson Cancer Center, Houston 77030, USA.  
NC AR 40335 (NIAMS)  
AR 42909 (NIAMS)  
SO JOURNAL OF CELL SCIENCE, (1995 Dec) 108 ( Pt 12) 3677-84  
Journal code: HNK. ISSN: 0021-9533.  
CY ENGLAND; United Kingdom  
DT Journal, Article; (JOURNAL ARTICLE)

LA English  
FS Priority Journals  
EM 199705  
EW 19970502  
AB Type II collagen is a major chondrocyte-specific component of the

cartilage extracellular matrix and it represents a typical differentiation marker of mature chondrocytes. In order to delineate cis-acting elements of the mouse pro alpha 1(II) collagen gene that control chondrocyte-specific expression in intact mouse embryos, we generated transgenic mice harboring chimeric constructions in which varying lengths of the promoter and intron 1 sequences were linked to a beta-galactosidase reporter gene. A construction containing a 3,000 bp promoter and a 3,020

bp intron 1 fragment directed high levels of beta-galactosidase expression specifically to chondrocytes. Expression of the transgene coincided with the temporal expression of the endogenous gene at all stages of embryonic development. Successive deletions of intron 1 delineated a 182 bp fragment which targeted beta-galactosidase expression to chondrocytes with the same specificity as the larger intron 1 fragment. Transgenic mice harboring a 309 bp \*\*\*Col2a1\*\*\* \*\*promoter\*\*\* lacking intron 1 tester sequences showed no beta-galactosidase expression in chondrocytes.

Reduction of the 182 bp fragment to a 73 bp subfragment surrounding a decamer sequence previously reported to be involved in chondrocyte specificity, resulted in loss of transgene expression in chondrocytes. When the \*\*\*Col2a1\*\*\* \*\*promoter\*\*\* was replaced with a minimal beta-globin promoter, the 182 bp intron 1 sequence was still able to target expression of the transgene to chondrocytes. We conclude that a 182 bp intron 1 DNA segment of the mouse Col2a1 gene contains the information to confer high-level, temporally correct, chondrocyte expression on a reporter gene in intact mouse embryos and that \*\*\*Col2a1\*\*\* \*\*promoter\*\*\* sequences are dispensable for chondrocyte expression.

L63 ANSWER 10 OF 12 MEDLINE DUPLICATE

AN 94175898 MEDLINE  
DN 94175898

TI Synthesis of recombinant human procollagen II in a stably

transfected

tumour cell line (HT1080)  
AU Fertala A, Sieron A L; Ganguly A; Li S W; Ala-Kokko L; Anumula K R; Prockop D J  
CS Department of Biochemistry and Molecular Biology, Jefferson Institute of Molecular Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107.  
NC AR38188 (NIAMS)  
SO BIOCHEMICAL JOURNAL, (1994 Feb 15) 298 ( Pt 1) 31-7.  
Journal code: 9YO. ISSN: 0264-6021.

CY ENGLAND; United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)

LA English  
FS Priority Journals; Cancer Journals  
EM 199406  
AB Apparently because the biosynthetic pathways involve eight or more highly specific post-translational enzymes, it has been difficult to obtain expression of genes for fibrillar collagens in recombinant systems.

Here two constructs of the human gene for procollagen II (COL2A1) were prepared, one with about 0.5 kb of a promoter for a procollagen I

(COL1A1) and the other with about 4 kb of the promoter for the procollagen II gene. The constructs, together with a neomycin-resistant gene, transfected into a human tumour cell line (HT1080) that synthesizes the collagen IV found in basement membranes, but does not synthesize any

fibrillar collagen. About two per 100 clones resistant to the neomycin analogue G418 synthesized and secreted human procollagen II. Milligram quantities of the recombinant procollagen II were readily isolated from the cultured medium. The recombinant procollagen II had the expected amino acid sequence as defined by nucleotide sequencing of mRNA-derived cDNA and the expected amino acid composition as defined by analysis of

procollagen II that was converted into collagen II by digestion with procollagen N- and C-proteinases. Also, analysis of the carbohydrate content indicated that there was glycosylation of some of the hydroxyllysine residues but no evidence of post-translational overmodification of the residues. In addition, the protein was shown to have a native conformation as assayed by a series of protease digestions. No essential differences were found

between clones transfected with the COL2A1 gene construct containing the COL1A1 promoter and the similar construct containing the \*\*\*COL2A1\*\*\*

\*\*promoter\*\*\* in terms of number of clones synthesizing recombinant procollagen II and the levels of expression. With both constructs, the expression of the COL2A1 gene was closely related to copy number. The results demonstrated therefore that it is not essential to use a promoter for a gene normally expressed in a host cell in order to obtain gene copy-number-dependent expression of an exogenous collagen gene in stably transfected cells.

L63 ANSWER 11 OF 12 CAPLUS COPYRIGHT 1999 ACS  
AN 1994:185638 CAPLUS  
DN 120:185638  
TI Synthesis of recombinant human procollagen II in a stably transfected

tumor cell line (HT1080)  
AU Fertala, Andrzej; Sieron, Aleksander L.; Ganguly, Arupa; Li, Shi-Wu; Ala-Kokko, Leena; Anumula, Kalyan R.; Prockop, Darwin J. CS Jefferson Med. Coll., Thomas Jefferson Univ., Philadelphia, PA, 19107, USA  
SO Biochem. J. (1994), 298(1), 31-7  
CODEN: BJOOAK, ISSN: 0306-3275  
DT Journal  
LA English  
AB Apparently because the biosynthetic pathways involve eight or more highly specific post-translational enzymes, it has been difficult to obtain expression of genes for fibrillar collagens in recombinant systems.

Here two constructs of the human gene for procollagen II (COL2A1) were prepd., one with about 0.5 kb of a promoter for a procollagen I gene (COL1A1) and the other with about 4 kb of the promoter for the procollagen II gene.

The constructs, together with a neomycin-resistant gene, were transfected into a human tumor cell line (HT1080) that synthesizes the collagen IV found in basement membranes, but does not synthesize any fibrillar collagen. About two per 100 clones resistant to the neomycin analog G418 synthesized and secreted human procollagen II. Milligram quantities of the recombinant procollagen II were readily isolated from the cultured medium. The recombinant procollagen II had the expected amino acid sequence as defined by nucleotide sequencing of mRNA-derived

cDNA and the expected amino acid composition as defined by analysis of procollagen II that was converted into collagen II by digestion with procollagen N- and C-proteinases. Also, analysis of the carbohydrate content indicated that there was glycosylation of some of the hydroxyllysine residues but no evidence of post-translational overmodification of the residues. In addition, the protein was shown to have a native conformation as assayed by a series of protease digestions. No essential differences were found

between clones transfected with the COL2A1 gene construct containing the COL1A1 promoter and the similar construct containing the \*\*\*COL2A1\*\*\*

\*\*promoter\*\*\* in terms of number of clones synthesizing recombinant procollagen II and the levels of expression. With both constructs, the expression of the COL2A1 gene was closely related to copy number. The results demonstrated therefore that it is not essential to use a promoter

for a gene normally expressed in a host cell in order to obtain gene copy-number-dependent expression of an exogenous collagen gene in stably transfected cells.

L63 ANSWER 10 OF 12 MEDLINE DUPLICATE  
AN 94175898 MEDLINE  
DN 94175898  
TI Synthesis of recombinant human procollagen II in a stably

COL2A1 genes were sequenced. With the assumption that these motifs should be well conserved during evolution, a search was made for potential elements important for the tissue-specific transcription of the COL2A1 gene by aligning the 2 sequences with each other and with the available rat type-II procollagen sequence for the promoter. With the assumption that these motifs should be well conserved during evolution, a search was made for potential elements important for the tissue-specific transcription of the COL2A1 gene by aligning the 2 sequences with each other and with the available rat type-II procollagen sequence for the promoter. Specific evolutionarily well-conserved motifs in the promoter area were identified. However, several suggested regulatory elements in the promoter region did not show evolutionary conservation. However, several suggested regulatory elements in the promoter region did not show evolutionary conservation. In the middle of the first intron was a cluster of well-conserved transcription-control elements, these motifs most probably possess a significant function in the control of the tissue-specific transcription of the COL2A1 gene. In the middle of the first intron was a cluster of well-conserved transcription-control elements; these conserved motifs most probably possess a significant function in the control of the tissue-specific transcription of the COL2A1 gene. Locations of adml, highly conserved nucleotide stretches were identified which are good candidate regions in the search for binding sites of yet-uncharacterized cartilage-specific regulators of the COL2A1 gene. Locations of adml, highly conserved nucleotide stretches were identified which are good candidate regions in the search for binding sites of yet-uncharacterized cartilage-specific regulators of the COL2A1 gene.

L1	FILE 'MEDLINE' ENTERED AT 15:12:49 ON 18 OCT 1999
L2	142 S STROMA#(P)EXOGENOUS GENE OR GENE
L3	CONSTRUCT OR VECTOR/AB,BI
L4	26 S L1 AND PROMOTER#/AB,BI
L5	1 S L2 AND COLLAGEN/AB,BI
L6	14675 S MESENCHYM#7/AB,BI
L7	64 S L4(P)GENE CONSTRUCT OR EXOGENOUS
L8	GENE OR VECTOR#/AB,BI
L9	12 S L5 AND PROMOTER#/AB,BI
L10	443 S STROMAL FIBROBLAST#/AB,BI
L11	11 S L7(P)VECTOR# OR CONSTRUCT#/AB,BI
L12	398 S OBESITY GENE OR OBESITY PROTEIN OR OB
L13	GENE/AB,BI
L14	1 S L9(L10A)XCONSTRUCT OR VECTOR/AB,BI
L15	0 S OB GENE AND (MESENCHYMAL OR MARROW
L16	STROMA# OR STROMAL FIBROBL
L17	69 S L7M/C#
L18	0 S L12 AND OB GENE/AB,BI
L19	0 S L12 AND OBESITY FACTOR/AB,BI
L20	9 S OBESITY FACTOR/AB,BI
L21	1867 S LEPTIN/AB,BI
L22	385 S L16 AND ADIPOCYTE#/AB,BI
L23	8138 S ADIPOCYTE#/AB,BI
L24	54 S L18(L10A)XCONSTRUCT OR EXOGENOUS OR
L25	VECTOR/AB,BI
L26	1 S L19 AND (OB GENE OR LEPTIN)/AB,BI
L27	14812 S L1 OR L4
L28	0 S L21 AND (OB GENE OR LEPTIN)/AB,BI
L29	FILE 'MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS'
L30	ENTERED AT 15:28:51 ON 18
L31	OCT 1999
L32	2 S L22
L33	2 DUP REM L23 (0 DUPLICATES REMOVED)
L34	9653 S OBESITY PROTEIN OR OBESITY FACTOR OR
L35	OBESITY GENE OR OB GENE
L36	1681 S L25 AND (STROMA# OR MESENCHYMAL OR
L37	ADIPOCYTE#/AB,BI
L38	363 S L25 AND (CONSTRUCT# OR VECTOR# OR
L39	EXOGENOUS)/AB,BI
L40	79 S L27 AND (STROMA# OR MESENCHYMAL OR
L41	ADIPOCYTE#/AB,BI
L42	35 DUP REM L28 (44 DUPLICATES REMOVED)
L43	E PROCKOP DARWIN J/AU
L44	553 S E3-E4
L45	18 S L30 AND (MARROW STROMA# OR
L46	MESENCHYMAL)/AB,BI
L47	12 DUP REM L31 (6 DUPLICATES REMOVED)
L48	0 S L32 AND PROMOTER#/AB,BI
L49	E PEREIRA RUTH F/AU
L50	26 S E2-E4
L51	20 DUP REM L34 (6 DUPLICATES REMOVED)
L52	3 S L35 AND (MARROW STROMA# OR
L53	MESENCHYMAL)/AB,BI
L54	3 DUP REM L36 (0 DUPLICATES REMOVED)
L55	E LEEPER DENNIS B/AU
L56	40 S E2-E3
L57	

Host Name: +++  
OK  
ATHZ  
OK

L39 2 S L38 AND (MARROW STROMA# OR  
MESENCHYMAL)/AB.BI  
L40 1 DUP REM L39 (1 DUPLICATE REMOVED)  
E OHARA MICHAEL D/AU  
E KULKOSKY JOSEPH/AU  
L41 79 S E1-E5  
L42 0 S L41 AND (MARROW STROMA# OR  
MESENCHYMAL)/AB.BI  
E PHINNEY DONALD/AU  
L43 26 S E3-E5  
L44 7 S L43 AND (STROMA# OR MESENCHYMAL)/AB.BI  
L45 6 DUP REM L44 (1 DUPLICATE REMOVED)  
E LAPTEV ALEXEY/AU  
L46 15 S E1-E4  
L47 5 S L46 AND (STROMA# OR MESENCHYMAL)/AB.BI  
L48 4 DUP REM L47 (1 DUPLICATE REMOVED)  
L49 163 S (STROMA#X)10AXPROMOTER#/AB.BI  
L50 4 S L49(10A)XCOLLAGEN/AB.BI  
L51 1 DUP REM L50 (3 DUPLICATES REMOVED)  
L52 0 S L49(10A)XPROCOLLAGEN OR COL1A1 OR  
COL2A1)/AB.BI  
L53 200 S (PROCOLLAGEN OR COL1A1 OR  
COL2A1)XWXPROMOTER#/AB.BI  
L54 0 S L53(X)OBESITY GENE OR OB GENE OR  
OBESITY PROTEIN OR LEPTIN)  
L55 0 S L53(10A)XSTROMA# OR MESENCHYMAL)/AB.BI  
L56 0 S L53(10A)XMARROW/AB.BI  
L57 4 S L53(X)STROMA# OR MESENCHYMAL)/AB.BI  
L58 1 DUP REM L57 (3 DUPLICATES REMOVED)  
L59 29 S L53(X)BONE CELL# OR OSTEOBLAST# OR  
PREOSTEOBLAST#/AB.BI  
L60 8 DUP REM L59 (21 DUPLICATES REMOVED)  
L61 893 S COL2A1/AB.BI  
L62 24 S COL2A1 PROMOTER/AB.BI  
L63 12 DUP REM L62 (12 DUPLICATES REMOVED)

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	ENTRY	SINCE FILE	TOTAL
FULL ESTIMATED COST	SESSION	320.92	338.48

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)  
SINCE FILE TOTAL

CA SUBSCRIBER PRICE	ENTRY	SESSION
	-10.71	-10.71

STN INTERNATIONAL LOGOFF AT 15:49:19 ON 18 OCT 1999